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Annotations

Pain relief

Do children feel pain?

It is not so long ago that clinicians felt that 'children seldom need medication for the relief of pain after general surgery'.[1] Twenty years ago in Chicago, only two out of 60 children received analgesia postoperatively. Similarly only 26 of the 180 children on an intensive care unit (where invasive procedures are common) received opiate analgesia.[1] That children feel pain but do not complain of it was shown by Mather and Mackie who interviewed 170 children recovering from surgery.[2] Seventy (40%) reported moderate or severe pain on the day of the operation. Children would read or watch TV in order to distract themselves from the pain. They would therefore appear to be pain free, whereas on direct questioning they would confess to having pain.[2]

Many theoretical reasons have been proposed as to why the newborn infant may not feel pain.[3] Anand and co-workers, however, have shown that preterm babies in response to surgery have biochemical changes consistent with stress.[4] These biochemical changes were reduced by administration of opiate analgesia (fentanyl). Also, babies receiving analgesia had fewer postoperative complications.

Do doctors prescribe appropriate analgesia?

Several studies have shown that it is not uncommon for children to have no analgesia prescribed postoperatively, even after major cardiac surgery.[2 5] Children are more likely to be prescribed weaker analgesia than adults undergoing similar surgery.[5] A recent questionnaire showed that although 80% of paediatric anaesthetists believe that neonates feel pain, only 11% would usually prescribe opiate analgesia after major surgery.[6] Over 40% were reluctant to prescribe opiate analgesia for infants up to the age of 3 months. It is quite clear that many doctors are frightened of the clinical effects of opiate analgesia despite the paper by Anand and co-workers, which showed that opiate analgesia s not only safe but also actually *reduces* complications.

Do nurses administer prescribed analgesia?

Our fear of the effects of opiates in children has been conveyed to the nursing profession. In the study by Mather and Mackie, 39% of opiates prescribed were not given.[2] In 29% of cases a weaker analgesic was given and it would appear that nurses feel it is safer for the patient to receive the less potent analgesic where more than one drug is prescribed. Adults received more than twice as many analgesics as children after major cardiac surgery.[5] On the fifth postoperative day, 50 adults received a total of 136 doses of analgesics whereas an equal number of children received a total of 10 doses of analgesics. Children received on average two doses each day during the first three postoperative days. It is young children who suffer the most. The 12 children who received no analgesia postoperatively were all infants and toddlers.[5]

Opiate infusions

The use of a continuous infusion of morphine in children was first described by Miser *et al* in 1980.[7] Eight children with terminal malignancy and severe pain unresponsive to both oral and intermittent opiates were successfully treated with morphine infusions. Both children[8] and adults[9 10] have less pain postoperatively when given a morphine infusion than with intermittent morphine. The safety of opiate infusions is shown by the experience in Perth where over 600 children have been treated and only one child required naloxone.[11] The advantage of an infusion is that as well as *preventing* pain (rather than waiting for a patient to complain of pain and then administering analgesia), it also avoids painful intramuscular injections which for some children are as distressing as the pain itself.

Are neonates and infants sensitive to opiates?

There is some evidence to suggest that children under the age of 6 months are more sensitive to opiates. The newborn infant in particular may be more sensitive to respiratory depression with morphine than adults.[12] Irregular breathing and seizures have been reported in infants and neonates receiving a morphine infusion.[8 13] Other papers have, however, suggested that morphine is safe in the neonatal period.[14–16] The neonate may also be more sensitive to fentanyl.[17]

Morphine metabolism

The half life of morphine in plasma is greater in newborn infants than in older infants because of reduced clearance.[15] Lower doses of morphine in neonates would therefore appear to be rational. The situation is however complicated by the formation of morphine-6-glucuronide and morphine-6-sulphate, both active metabolites of morphine. Both are more potent analgesics than morphine in animals.[18 19] Morphine-6-glucuronide is an effective analgesic when given to adults,[20] and is present in plasma in higher concentrations than morphine itself after repeated oral administration of morphine.[21] The formation of morphine-6-glucuronide is likely to be reduced in neonates as glucuronidation of other drugs is impaired in the neonatal period. Also, in vitro studies with fetal liver show a reduced ability to form morphine glucuronides.[22] Little is known of the metabolism of morphine in neonates or children, or of the respective roles played by morphine, morphine-6-glucuronide, and morphine-6-sulphate in relation to analgesia and respiratory depression. As well as differences in the metabolism of opiates, animal studies have shown that opiate receptors may not be fully developed in the neonatal period.[23]

Conclusion

It is clear that the present management of pain relief in children can be improved considerably. Opiate infusions should be used more frequently in the postoperative period. Morphine is probably the drug of choice in that it has been used extensively and is both safe and effective. The protocol developed by Bray involves a morphine infusion of 20 μg/kg/hour, and if no opiate has been given with the premedication, an initial bolus dose of 200 μg/kg. The infusion is usually required for 24 to 48 hours and the infusion rate adjusted for each individual patient.

Neonates receiving mechanical ventilation tolerate the same infusion rate of morphine (20 μg/kg/hour) after surgery or painful procedures (for example, insertion of pneumothorax drain). For spontaneously breathing neonates, however, intensive monitoring must be utilised in view of the possibility of respiratory depression.[24] In these babies and also in infants under the age of 12 months it is probably advisable to use an initial lower dose of morphine (10 μg/kg/hour) until our understanding of analgesia in infancy has improved.

Dr Choonara is an MRC Travelling Fellow.

References

[1] Swafford LI, Allan D. Pain relief in the pediatric patient. *Med Clin North Am* 1968;**52:**131–6.

[2] Mather L, Mackie J. The incidence of postoperative pain in children. *Pain* 1983;**15:**271–82.

[3] Hatch DJ. Analgesia in the neonate. *Br Med J* 1987;**294:**920.

[4] Anand KJS, Sippell WG, Aynsley-Green A. Randomized trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987;**i:**243–7.

[5] Beyer JE, DeGood DE, Ashley LC, Russell GA. Patterns o postoperative analgesic use with adults and children following cardiac surgery. *Pain* 1983;**17:**71–81.

[6] Purcell-Jones G, Dormon F, Sumner E. Paediatric anaesthetists' perceptions of neonatal and infant pain. *Pain* 1988;**33:**181–7.

[7] Miser AW, Miser JS, Clark BS. Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. *J Pediatr* 1980;**96:**930–2.

[8] Bray RJ. Postoperative analgesia provided by morphine infusion in children. *Anaesthesia* 1983;**38:**1075–8.

[9] Church JJ. Continuous narcotic infusions for relief of postoperative pain. *Br Med J* 1979;**i:**977–9.

[10] Rutter PC, Murphy F, Dudley HAF. Morphine: controlled trial of different methods of administration for postoperative pain relief. *Br Med J* 1980;**280:**12–3.

[11] Dilworth NM, MacKeller A. Pain relief for the pediatric surgical patient. *J Pediatr Surg* 1987;**22:**264–6.

[12] Way WL, Costley EC, Way EL. Respiratory sensitivity of th newborn infant to meperidine and morphine. *Clin Pharmaco Ther* 1965;**6:**454–61.

[13] Koren G, Butt W, Chinyanga H, Soldin S, Tan YK, Pape K. Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J Pediatr* 1985; **107:**963–7.

[14] Duncan A. The postoperative period. *Clinics in Anaesthesiolog* 1985;**3:**619–32.

[15] Lynn AM, Slattery JT. Morphine pharmocokinetics in earl infancy. *Anesthesiology* 1987;**66:**136–9.

[16] Purcell-Jones G, Dormon F, Sumner E. The use of opioids in neonates. A retrospective study of 933 cases. *Anaesthesi* 1987;**42:**1316–20.

[17] Koehntop DE, Rodman JH, Brundage DM, Hegland MG Buckley JJ. Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986;**65:**227–32.

[18] Shimomura K, Kamata O, Ueki S, *et al.* Analgesic effect o morphine glucuronides. *Tohoku J Exp Med* 1971;**105:**45–52.

[19] Mori M, Oguri K, Yoshimura H, Shimomura K, Kamata O Ueki S. Chemical synthesis and analgesic effect of morphine ethereal sulfates. *Life Sci* 1972;**11:**525–33.

[20] Osborne R, Joel S, Trew D, Slevin M. Analgesic activity o morphine-6-glucuronide. *Lancet* 1988;**i:**828.

[21] Säwe J, Svensson JO, Rane A. Morphine metabolism in cancer patients on increasing oral doses—no evidence for autoinduction or dose-dependence. *Br J Clin Pharmacol* 1983;**16:**85–93.

[22] Pacifici GM, Säwe J, Kager L, Rane A. Morphine glucuronidation in human fetal and adult liver. *Eur J Clin Pharmaco* 1982;**22:**553–8.

[23] Leslie FM, Tso S, Hurlbut DE. Differential appearance of opiate receptor subtypes in neonatal rat brain. *Life Sci* 1982;**31:** 1393–6.

[24] Yaster M. Analgesia and anesthesia in neonates. *J Pediatr* 1987;**111:**394–6.

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Archives of Disease in Childhood, 1989, **64,** 1103–1104

Does early intervention 'work'?

Proponents of American Head Start programmes in the 60s and early 70s promised boldly that preschool attendance would increase the intelligence, school attainment, and self concept of disadvantaged children. Similar optimism lay behind the British Educational Priority Area programmes that were aimed at eradicating social inequality by helping children from poor families to participate at school on an equal footing with their more privileged peers.[1] The first wave of evaluation studies on both sides of the Atlantic was so cheering that optimism reigned for several years. Then came the disappointing 'wash-out' research, notably the Westinghouse study showing a grim picture of 'extra' skills which disappeared three to four years after children left the preschool.[2]

There was much pessimism about early education until a group of American researchers began a rigorous study of the long term effects of compensatory education.[3] They ignored 'garden variety' programmes (which excluded most of the federally funded Head Start) and focused instead on intervention projects that employed rigorous research designs. Lazar *et al* limited the follow up study to the effects of preschool projects with sample size greater than 100 children, which employed quantitative assessment measures, comparison or control groups, and follow up after children entered school. By these strict criteria 11 carefully monitored programmes were chosen for follow up study. Approximately 2000 preschool 'graduates' were tracked down in adolescence and researchers investigated their school and employment records, as well as interviewing their families.

Results showed clearly that attendance at excellent, cognitively orientated preschool programmes was associated with later school competence. More specifically, preschool graduates were less likely to be assigned to 'special' schools or to be retained in grade. At interview, researchers found that preschool graduates were more likely than controls to give achievement related answers to the invitation 'tell me something you've done that made you feel proud'. The interviews with children and parents showed that early education affected the achievement orientation of the entire family, giving the child confidence in his own self efficacy.[4]

The most carefully controlled of all 11 programmes reviewed by Lazar *et al* was the High/Scope project.[5] The table summarises the main findings on 123 children who were followed up to the age of 19. A sophisticated cost-benefit analysis was carried out and it showed that 'for every $1000 that was invested in the preschool programme, at least $4130 (after inflation) has been or will be returned to society'.[6] These calculations were based on the financial cost to society of juvenile delinquency, remedial education, and joblessness—set against the running costs of an excellent preschool programme.

Although American studies cannot prove that *all* preschool programmes will cause lasting improvements, they *do* demonstrate that early education can

Table *Major findings at age 19 in the High/Scope study (n=123)*[1]

Category	*Group*		
	Attended preschool	*Did not attend preschool*	*p Value*
% Employed (n=121)	59	32	0·032
% High school graduate (or its equivalent) (n=121)	67	49	0·034
% With college or vocational training (n=121)	38	21	0·029
% Ever detained or arrested (n=121)	31	51	0·022
Females only: teen pregnancies/100 (n=49)	64	117	0·084
Functional competence (APL survey: possible score 40) (n=109)	24·6	21·8	0·025
% Of years in special education (n=112)	16	28	0·039

change the course of children's lives.[7] Furthermore the High/Scope study strongly suggests that the mechanism for increasing school competence and employment is the child's positive attitude towards achievement and parents' increased aspiration for their offspring. The vigour of the American research, coupled with a plausible theoretical model, justifies optimism about cognitively structured programmes. But do they affect all children equally? The most recent research on Head Start in the United States suggests that the children who benefit most from preschool are those from the most disadvantaged backgrounds.[8]

There is less longitudinal research in Britain. The massive Child Health and Education (CHES) study gives cause for concern by showing great variation in the social backgrounds of children who attend different forms of provision; the better off go to playgroup and the most disadvantaged attend day nursery.[9] McGuire and Richman have documented greater severity of behaviour problems in the day nursery population, when compared with many nursery schools or playgroups. The CHES study has shown that children who attend day nursery go on to careers as poor readers and mathematicians in school.

The picture is now fully drawn: (a) educationally oriented preschool programmes can prevent cognitive and behavioural problems later in life[11]; (b) the children most at risk of behavioural and intellectual problems attend day care provision; and (c) there is an urgent need to improve educational provision in day nurseries if the 'life chances' of so many disadvantaged children are to be improved.[12]

References

[1] Smith G, James T. The effects of preschool education: some American and British evidence. *Oxford Review of Education* 1975;**1**:233–40.

[2] Westinghouse Learning Corporation. *The impact of Head Start: an evaluation of Head Start on children's cognitive and affective development.* Report prepared for the Office of Economic Opportunity, 1969. (Contract B89–4536.) (Westinghouse study.)

[3] Lazar I, Darlington R, Murray H, Royce J, Snipper A. Lasting effects of early education: a report from the consortium for longitudinal studies. *Monographs of the Society for Research in Child Development* 1982;**47**:2–3 (Serial No 195).

[4] Rutter M. Family and school influences on cognitive development. *J Child Psychol Psychiatry* 1985;**26**:683–704.

[5] Berrueta-Clement J, Schweinhart LJ, Barnett WS, Epstein AS, Weikart DP. Changed lives: the effects of the Perry preschool programme on youths through age 19. *Monographs of the High/Scope Educational Research Foundation* 1984, No 8.

[6] Breedlove C, Schweinhart LJ. *The cost-effectiveness of high quality early childhood programs.* A report for the 1982 Southern Governors' Conference, South Carolina, 1982.

[7] Woodhead M. Preschool education has long term effects but can they be generalised? *Oxford Review of Education* 1985;**11**: 133–56.

[8] Lee V, Brooks-Gunn J, Schnur E. Does Head Start work? *Developmental Psychology* 1988;**24**:210–22.

[9] Osborn AF, Milbank JE. *The effects of early education.* Oxford: Clarendon Press, 1987.

[10] McGuire J, Richman N. The prevalence of behaviour problems in three types of preschool group. *J Child Psychol Psychiatry* 1986;**27**:455–72.

[11] Offord DR. Prevention of behavioural and emotional disorders in children. *J Child Psychol Psychiatry* 1987;**28**:9–19.

[12] Education, Science and Arts Committee. *Educational provision for the under fives.* London; HMSO, 1989.

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Original articles

Click evoked otoacoustic emissions compared with brain stem electric response

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SUMMARY The hearing of 346 babies taken largely from a neonatal intensive care unit has been tested by otoacoustic emissions and brain stem electric response audiometry. A total of 336 (97%) of the babies have been followed up by hearing tests from the age of 8 months. The otocoustic emission test has been found to be practical with a mean test time of 12·1 minutes compared with 21·0 minutes for brain stem electric response. An otoacoustic emission was recorded bilaterally in 274 (79%) babies. Twenty of the 21 surviving infants who failed brain stem electric response in the neonatal period did not produce an emission. It is concluded that the otoacoustic emission test would make a good first screen to be followed by the brain stem electric response if no otoacoustic emission was present. There is poor agreement between the test results in the neonatal period and those of the follow up period, however, indicating the need for continuous monitoring of those babies failed by brain stem electric response.

Infants are not normally screened for hearing impairment before the age of 8 months when the ability to localise sounds is used. It is now generally agreed that the detection of hearing impairment before this age is desirable. Reports in the literature on the success of this screen at 8 months to detect a high proportion of the severely hearing impaired vary—for example, Newton reports a success rate of only 55%,[1] whereas McCormick indicates that a high success rate can be achieved with good organisation and training.[2] The advent of equipment that measures such reflexes as movement, startle, and respiration and the use of the brain stem electric response has led to many studies of hearing at birth with varying degrees of success. For example Murray *et al*, in their review of the use of the brain stem electric response test, report a confirmation rate of 4·8 to 100% of hearing impaired from follow up studies of infants who failed the brain stem electric response test at birth.[3]

Recently another possible method of detecting hearing impairment at birth has arisen, that of click evoked otoacoustic emissions. The phenomenon was first reported by Kemp in 1978.[4] Since then there have been many studies showing that the click evoked otoacoustic emission can be recorded in most normally hearing adults and more recently in normal newborns and in babies admitted to a special care unit.[5–7] It has also been shown that the click evoked emission is not present in adults when the hearing loss exceeds about 15 dB.[4 8–10] The question remains as to whether it is possible to use the otoacoustic emission to identify the hearing impaired newborn infant. Since May 1985 we have been carrying out a prospective study to investigate this. As in other studies we have selected babies admitted to a neonatal intensive care unit as being a convenient test group where the incidence of hearing impairment is known to be higher than in the whole population.

One problem of prospective studies is that there is evidence that some hearing impairments detected by tests at birth appear to improve with age,[3] and others may appear later on in the first year of life.[11] To enable the results of the otoacoustic emission test to be compared with a second test at birth, brain stem electric response was carried out at the same time.

In an earlier paper we published results of tests on 30 normal newborns and preliminary results on the first 112 infants in the prospective study.[7] This paper presents the results on the first 346 babies who have entered the study and who have been followed up to at least 12 months of age.

Subjects and methods

The aim of the prospective study was to test all babies admitted to the North Trent Neonatal Intensive Care Unit at the Jessop Hospital for Women in Sheffield. In practice only a proportion of the babies could be tested. In addition a small number of babies considered to be at risk of hearing impairment were tested as outpatients. During the period of testing reported here (August 1985–September 1987) 43·3% of babies admitted were tested as inpatients before leaving the unit and a further 8·7% on recall as outpatients giving a total of 52%. Excluding the 9·5% who died and the 1·6% who were in the unit for non-medical reasons there were several reasons for not testing the remaining 36·9%. A total of 15·8% were only in for 48 hours and were not tested as the risk of hearing impairment was considered to be no different to normal newborns, 11·3% were missed but considered by the paediatrician to be at low risk and so not recalled, and 9·8% who had been transferred back to their referring unit could not be recalled.

The mean birth weight was 2220 g (range 540–4890) and the mean gestational age 34 weeks (range 24–42). The mean postconceptional age when tested was 37·5 weeks (range 32–49) for inpatients and 47 weeks (range 40–59) for outpatients.

Both ears of each baby were tested by otoacoustic emission and brain stem electric response. The tests were carried out as near as possible to the time at which the baby left the unit. If the baby was transferred to the referring unit when too young or too sick to test it was recalled, if possible, to be tested as an outpatient. Any baby that failed to produce a brain stem electric response at or below 43 dB normal hearing level (nHL) in one ear and 53 dBnHL in the other was recalled for a further brain stem electric response test. Initially the criteria was 43 dBnHL in either ear but this produced too many requiring a retest. It was argued that the modified criteria was acceptable as the management of the child would be unaffected by this change. Where possible a retest was carried out while the baby was still in the unit, otherwise it was carried out on an outpatient basis at 4–6 weeks corrected age (that is, post due date). Tympanometry was attempted as a means of investigating middle ear disease, but was abandoned as being too difficult to carry out on all babies. The methods for otoacoustic emission and brain stem electric response recording have been given in an earlier paper.[7] The only modification since then was on the scoring of the recorded waveforms. The decision on the presence of a response was first made by the tester and an experienced user scoring independently. Where there was a disagreement then a third experienced user of these tests, scoring independently, was used to arbitrate.

All babies entering the study were recalled for distraction testing and tympanometry at 8 months corrected age. To pass the distraction test the baby had to elicit a full head turn to a range of stimuli covering the audiometric frequencies. It was intended that the persons involved in this follow up should have no knowledge of the results at birth. Although this was the case for most babies, in a few instances, particularly where the tests at birth had involved considerable follow up, it was possible that the tester could gain some knowledge of the results at birth. All babies not passing the distraction test at 30 dBnHL in each ear were recalled at approximately three to six month intervals until they were passed at this level.

Table 1 *Neonatal screen and follow up tests to 3 months corrected age*

	First screen (n=346)*	*Second test (n=42)*	*Final outcome (n=346)*
No (%) with no otoacoustic emission	72 (20·8)		
No (%) who passed BSER		18 (5·2)	323 (93·3)
No (%) who failed BSER‡	42 (12·1)	9 (2·6)	23 (6·6)§
No (%) with no otoacoustic emission:			
Who failed BSER	30 (8·7)		
Who passed BSER	42 (12·1)		
No (%) with otoacoustic emission present:			
Who failed BSER	12 (3·5)		
Who passed BSER	262 (75·7)		
Not tested		12 (3·5)	
Did not attend		2 (0·6)	
Died		1 (0·3)	2 (0·6)
Risk:‖			
Low			11 (3·2)
High			12 (3·5)

BSER=brain stem electric response.
*Fifteen were excluded from trial.
‡The pass criteria for the BSER test was a response at 43 dBnHL in one ear and 53 dBnHL in the other.
§The figure of 23 who failed BSER includes the two who subsequently died.
‖High risk is defined as those who failed the final BSER result in the worse ear at ≥73 dBnHL if tested at a corrected age of less than one month plus those who failed at ≥63 dBnHL if tested at a corrected age of ≥1 month. Low risk are the remainder of the 23 who did not pass the BSER test.

Results

The results of the otoacoustic emission and brain stem electric response tests carried out in the neonatal period and the distraction tests carried out from 8 months corrected age are presented in tables 1–5. A total of 346 babies entered the trial between August 1985 and September 1987.

For inpatients the mean time taken for each test for a sample of 92 infants was 12·1 minutes (range 5–23) for the otoacoustic emission test and 21·0 minutes (range 11–50) for the brain stem electric response test. The mean values increased to 17·8 minutes (n=19) and 24·1 minutes (n=20) respectively for outpatients. The outpatients required an additional feeding time of approximately 20 minutes.

As the age of the infant increased the ability to carry out both tests successfully was reduced. Whereas between 0 and 6 weeks corrected age (post due date) the tests on all 61 babies were successful, between 7 and 12 weeks corrected age (n=39) and above 12 weeks (n=21) only 36 (92·3%) and 15 (71·4%) respectively were successful.

Table 2 *Follow up tests starting at 8 months of age*

	First distraction test screen (n=346)	*Outcome to date independent of number of tests (n=346)*
No (%) failed at (dBnHL):		
>30/30	98 (28·3)	
40/30 40/40	50 (14·5)	
40/50 50/50	25 (7·2)	
50/60 60/60	23 (6·6)	
No (%) passed at ≤30/30 (dBnHL)		283 (81·8)
No (%) failed at >30/30 (dBnHL)		45 (13·0)
Not able to test	8 (2·3)*	3 (0·9)*
Did not attend	10 (2·9)	10 (2·9)
Died	5 (1·4)†	5 (1·4)†

*Inconsistent (n=1), uncooperative (n=1).
†Three babies died between the neonatal tests and the screen at 8 months of age. They passed the brain stem electric response at birth on first testing.

Table 4 *Comparison of the final outcome of BSER tests carried out in the neonatal period with the otoacoustic emission screen*

	BSER final outcome				*Totals*
	Pass	*Fail (total)*	*Fail— low risk*	*Fail— high risk*	
Otoacoustic emission screen:					
Present	272	2	1	1+	274
Absent	51	21*	10	11+	72
Totals	323	23	11	12	346

BSER=brain stem electric response.
*Includes one child with otoacoustic emission and BSER failures on opposite ears.
†One child died from each of these groups.

Table 3 *Comparison of the tests carried out during the neonatal period and the follow up tests starting at 8 months*

	Neonatal tests				
	Otoacoustic emission (one test)		*BSER (final outcome)*		
	Present	*Absent*	*Pass*	*Fail*	*Totals*
No at final outcome who:†					
Passed ≤30/30 (dBnHL)	234	49	270	13 (8+5)*	283
Failed >30/30 (dBnHL)	28	17	38	7 (3+4)*	45
Not able to test	2	1	2	1 (0+1)*	3
Did not attend	8	2	10	0 (0+0)	10
Died	2	3	3	2 (0+2)*	5
Totals	274	72	323	23 (11+12)*	346

BSER=brain stem electric response.
*Figures in parentheses show division into high and low risk groups as defined in table 1.
†Final outcome at 8 months of age (distraction test).
If the pass level for the distraction test is raised by 10 dB or 20 dB then the total number of failures (column 5) reduces from 45 to 31 or 17. Of the 45 failing at 30 dBnHL 36 had abnormal middle ear pressures. The proportion of those with no otoacoustic emission or failing the BSER in the neonatal period who failed on follow up is significantly higher ($p<0\cdot02$ in each case by χ^2) then the proportion of those who passed in the neonatal period and failed on follow up.

Table 5 *Follow up of 12 infants at high risk of hearing impairment based on the result of BSER tests in neonatal period (definition in table 1)*

Patient No	*Otoacoustic emission Left/right*	*BSER screen Left/right*	*BSER final test (corrected age years·months)*	*Distraction screen*	*Distraction—final test (actual age, years·months)*	*Final outcome to date*
46	No/no	63/73	Did not attend	30/40	20/20 (1·11)	Pass
58	No/no	63/63	Did not attend	?50/?50	50/50 (1·11)	Fail, bilateral conductive*
65	No/yes	>83/>83	>63/>83 (0·3)	70/70	30/30 (1·2)	Pass
102	No/no	53/63	63/63 (0·3)	70/70	30/30 (BSER) (1·11)	Pass
116	No/no	53/73	43/63 (0·1)	40/40	30/30 (1·5)	Pass
159	Yes/no	53/?83	53/>83 (0·3)	Died	—	—
162	Yes/yes	73/53 (0·1)‡	—	Died	—	—
167	Yes/no	43/73 (0·2)‡	—	70/60	20/20 (1·4)	Pass
183	No/no	73/63	>83/43 (0·1)	Fail	?/?	Inconsistent results
224	Atresia/no	Atresia/43 (0·2)‡	—	Atresia/60	—	L, atresia R, inconsistent results
372	Yes/no	43/73	33/>83 (0·3)	60/NR†	50/NR† (1·0)	Unilateral sensorineural*
383	No/no	43/63 (0·3)‡	—	80/80	60/60 (1·3)	Bilateral mixed*

BSER=brain stem electric response.
*Nct yet confirmed by bone conduction tests.
†NR=no response.
‡Age of test (years·months) added where final test.

Discussion

Several studies have shown that the brain stem electric response threshold in neonates reduces with age when tested particularly up to 40 weeks' postconception.[12] We have therefore always tried to test the babies at the oldest age possible while still in the neonatal intensive care unit. In our study some infants leave the unit well before they are old or well enough to test, particularly if they are being transferred back to their referring unit. These babies were tested as outpatients where possible. One solution to this problem is to use a higher pass criteria if the baby is tested at a younger age. We rejected this solution as there is considerable variation in threshold at any age and the use of a higher pass level may reduce the number of hearing impaired babies detected.

Both tests have proved practical. The number of babies who had to be rejected from the study was only 15 compared with the 346 who were successfully tested. In all cases but one this was due to excessive activity at the time the test was attempted. We have previously reported the time it took to carry out each test[7]; this was based on a small sample early in the study. The results given in this paper are of a more detailed investigation carried out at a later date. The mean time to carry out an otoacoustic emission compares very favourably with the distraction test used to screen for hearing impairment at 8 months. It is also safe, non-invasive and, unlike the distraction test, only requires one tester. The brain stem electric response test requires longer, largely as a result of the time required to attach the electrodes. The results also show that, for this test, babies tested as outpatients at a mean corrected age of 7 weeks required only a slightly longer test time, although the total time was considerably longer due to the delays while the baby was being fed before the test. As the age increases, however, the results show that the proportion of babies who will not sleep for the test rises and a practical age limit for this method appears to be about 3 months. Although a higher proportion may fail either test while in the unit than at an older age, the additional costs of the latter in time and appointment procedure for the hospital and family and the problems of non-attendance mean that these screening tests (from a cost point of view) are best carried out before the infant leaves the unit.

One of the main questions of any screening procedure is—does it pass a sufficiently high proportion of the populations being tested? The results in table 1 show that 79% of the infants produce an otoacoustic emission in both ears on first testing. There was little change in the figures for sequential groups of 100 babies entering the study who produced an emission in both ears (81%, 78%, and 83%). Possible reasons why 21% do not produce an emission are discussed in our earlier report.[7] The pass rate of the brain stem electric response test is higher but, in a more detailed study (to be published), it was found to be very dependent on the stimulus level used for the pass criteria. For example at a pass level of 43 dBnHL in each ear the pass rate for the brain stem electric response test was found to be lower than the 79% for the otoacoustic emission test.

We were able to retest (table 1) 27 of the 42 babies who did not pass the first screen. The fact that two thirds of these passed on second testing indicates that on a two test brain stem electric response screen at the stimulus levels used in our study the final pass figure would be 96%. The final outcome of the brain stem electric response testing in the neonatal period left 23 infants who had not been passed. This group was further divided by the brain stem electric response threshold into a group at 'high risk' and 'low risk' of hearing impairment. Some babies who could not be recalled for further brain stem electric response tests had their last test at below a corrected age of 1 month. The criteria for the high risk group takes this into account by changing the criteria at 1 month of corrected age (see table 1). This is based on the reports in the literature that the brain stem electric response threshold reduces with age.[12]

There is a wide range of published values for failure rates for the brain stem electric response tests carried out on high risk infants at birth. In their review Murray *et al* give an average failure rate of 16·5% with a range of 9 to 39%.[3] We have shown that by retesting it is possible to reduce this figure to 6·6% and if we had retested all the infants to a predicted 4%. This figure is in close agreement with Nield *et al* who report an initial failure rate by brain stem electric response of 18·8% and a failure rate of 3·2% on retesting for 605 graduates of a neonatal intensive care unit.[11] As noted in the method section the brain stem electric response pass criteria we used—of 43 dBnHL in one ear and 53 dBnHL in the other—we consider to be reasonable to detect clinically important hearing impairment. It is clear from retrospective studies such as that by Newton,[1] however, that the long term incidence of sensorineural hearing impairment is much lower than these brain stem electric response failure rates would indicate. She found that the incidence of bilateral sensorineural hearing loss to be 0·08% overall. This increased to 0·5% of live births (1·1% of survivors) for babies of birth weight less than 1500 g. Our mean birth weight was 2220 g. A rate of between 0·08 and 1·1% would therefore be expected for bilateral sensorineural hearing loss; this is much lower than the brain stem electric response fail rate. Careful examination must therefore be made of those babies failing the brain stem electric response at birth to decide which are in this category and will need treatment.

The results of the first screen by the distraction test at 8 months show the highest failure rate of all three screening tests. Like the brain stem electric response test at birth the failure rate is very dependent on the stimulus level used. The number reduces by one half for a 10 dB rise in the pass criteria from 30 to 40 dBnHL (table 2).

The final outcome of the follow up tests to date leaves 45 infants who have not passed at 30 dBnHL, three who could not be tested, and 10 who could not be recalled. All of the latter passed the brain stem electric response test at birth. Although this figure is reducing as further tests are carried out, the 45 infants who did not pass represent twice the proportion of those not passed at birth. One possible reason for this could be that the pass criteria at 30/30 dBnHL will fail a higher proportion than that used for the brain stem electric response test (43/53 dBnHL). Raising the pass level by 10 dB reduces the number who failed from 45 to 31 and raising it by 20 dB reduces it to 17 (table 3). Whichever criteria is used, however, there is little agreement between the results at birth and those at 8 months, although the results show significance ($p<0{\cdot}02$ by χ^2, table 3). This is in contrast with the much closer association between the outcome of the otoacoustic emission screen and the brain stem electric response test at birth (table 4) ($p<0{\cdot}0001$ by χ^2). Twenty of the 21 infants who failed the brain stem electric response on final outcome and survived would have been detected by the otoacoustic emission screen. Note though that in one infant opposite results were obtained on the two ears for the brain stem electric response and otoacoustic emission tests. These results in table 4 produce sensitivity and specificity values of the otoacoustic emission test for brain stem electric response final outcome of 95% and 85% respectively.

A large proportion of the 45 infants not passed by the follow up tests to date had negative middle ear pressures (table 3). Only nine infants of this group were reported as having normal middle ear pressures. All of these nine passed the brain stem electric response on final outcome at birth.

The lack of agreement between the results in the neonatal period and those in the follow up period starting at 8 months corrected age raises the question of whether a prospective study can prove that the tests at birth are correct. Both the figures of 23 out of 346 at birth and 45 out of 346 at 8 months are high compared with the expected number for a neonatal intensive care unit population, as noted above, and must contain many false positives. The lack of agreement may simply be due to different causes of false positives in the neonatal period and in the follow up period. There are many reports in the literature of higher incidences than that reported here of hearing impairment in neonatal intensive care unit populations studied by brain stem electric testing. Murray *et al*, in their review of studies on brain stem electric response screening in the newborn, report a variation of between 1% and 22% in the number of 'hearing impaired' from follow up work.[3] The confirmation rate—that is, the proportion of brain stem electric response failures later confirmed as 'hearing impaired'—varied from 4·8% to 100%.

In the study by Galambos *et al* on babies from an intensive care nursery (which represents about half of the infants reviewed by Murray *et al* where the follow up work had been carried out) overall 16·1% failed the 30 dBnHL brain stem electric response screen at birth.[13] From the 54% of those that attended the retesting it was estimated that for the whole sample of 1613 infants unilateral and bilateral hearing impairments would be found in 2·8% and 6% respectively and hearing aids fitted to 4%. A figure of above 1:100, however, seems unlikely from a consideration of total population incidence and published retrospective data. McCormick *et al*, who studied the use of the auditory response cradle in a neonatal intensive care unit similar to ours,[14] found three bilateral sensorineural hearing impaired infants among the 396 tested, which is much closer to this figure than some of the high figures reported in the literature. The wide range of values reported by Murray *et al* for the percentage of hearing impaired (1–22%) and the wide range of confirmation rates of 4·8–100% indicate that the brain stem electric response test as a prognostic indicator of permanent hearing impairment is far from established.

Most studies on the use of brain stem electric response at birth involving large numbers of infants, reviewed by Murray *et al*,[3] have only followed up brain stem electric response failures. Nield *et al*, however, report 11 graduates of a neonatal intensive care unit who passed the brain stem electric response at birth (response at 30 dBnHL) and were subsequently found to be hearing impaired, and seven of these were profound.[11] There was, however, evidence of hearing in some of these infants later on in the first years of life. Galambos *et al* considered that false negatives would be rare.[13] This may be true in adults but the results of Nield *et al* suggest that when considering long term hearing impairment the use of results of the brain stem electric response carried out at birth may be limited.[11] Duara *et al* report on a sample of 278 infants tested by brain stem electric response at birth of whom 159 were from the intensive care nursery. They again show that false positives can occur.[15] Twenty seven of the 35 who failed the brain stem electric response screen at birth (no response at 35 dBnHL in either ear; pass if response at 35 dBnHL in first ear tested) had an initial audiological follow up between the ages of 4 and 17 months. Otological examination showed no abnormality suggestive of conductive hearing loss in any of these 27 infants. Ten of the 27 infants had abnormal hearing. In subsequent follow up six gradually improved and of the four that persisted three were fitted with hearing aids. Of the four who had no brain stem electric response at 80 dBnHL at birth, the follow up results were one normal, one gradual improvement, and two with persistent hearing impairment.

In our study none of the 12 infants who were classified as being at high risk of hearing impairment from the neonatal brain stem electric response tests (table 5) passed their 8 month screen, although two gave responses at or below 40/40 dBnHL. Five went on to pass at 30/30 dBnHL by the age of 2 years. Of the remaining five, one is thought to have a unilateral sensorineural hearing loss, one a bilateral mixed loss, one a bilateral conductive loss, and two have given inconsistent results and no conclusion has been reached to date. Baby number 65 illustrates the need for continuous follow up. No brain stem electric responses were recorded on three occasions in the neonatal period up to 83 dBnHL. At 10 months there were responses to low frequencies only at 70 dBnHL. The hearing threshold then appeared to improve and was normal by the age of 14 months. Baby 102 is a less extreme example of the same results. This sort of result is similar to some of those reported by Duara *et al* as noted above.[15] If the combination of otoacoustic emission and brain stem electric response or brain stem electric response on its own is to be used to screen for hearing impairment then it is clear that continuous monitoring of failures is required and no conclusions on the long term outlook must be drawn.

Although this report is only on the first 346 babies in our study, we are able to draw several useful conclusions on the application of the click evoked otoacoustic emissions and brain stem electric response audiometry to detect the hearing impaired at birth. Both tests pass a sufficient proportion to be considered as a screening procedure. Consideration of the shorter time required for the otoacoustic emission test, the detection of nearly all (20/21 who survived) of those who failed the brain stem electric response on the final outcome of the tests in the neonatal period, and it being less invasive that the brain stem electric response test indicate that it would make the better screening test. A brain stem electric response test carried out at the same time on babies not producing an otoacoustic emission would make a good complementary test. If this procedure were implemented our results indicate that, for the population tested in our study, 79% would pass the otoacoustic emission test. A further 12% would pass the brain stem electric response test carried out on those not producing an emission leaving 9% to be followed up. As the click evoked otoacoustic emission cannot determine the degree of hearing impairment then the brain stem electric response test would be used for this. The high pass rates and the low cost of carrying out the tests while the babies are still in the unit indicate that this is the best time at which to carry out the screening test.

The final outcome of the follow up tests to date, however, show poor correlation with the final outcome of the neonatal tests. For example only seven of the 21 surviving infants who failed brain stem electric response at birth failed on follow up (outcome to date) at 30 dBnHL. This was out of a total of 45. Raising the pass/fail level of the distraction test by 10 dB to 40 dBnHL did not alter this lack of agreement greatly (6/21, total 31). The difficulties of the distraction test are illustrated by the high proportion who fail on first testing, although this was found to be very dependent on the pass criteria. It is not yet possible to say how many hearing impaired babies we have missed until the 45 failures on follow up have been further tested. There are many possible explanations for this disagreement between tests carried out in the neonatal period and those on follow up—for example, undetectable responses, temporary middle ear disease, delayed neurological development. It must be concluded, however, that it is not possible to use the distraction test results to determine if the tests at birth were correct at that time.

In conclusion we have found that the otoacoustic emission can detect most of those infants who will not pass the brain stem electric response in the neonatal period, but it is clear that the prognostic value of brain stem electric response is not yet established. Any prospective study investigating the ability of these tests to detect hearing impairment at birth must follow up each failure at very frequent intervals if a fuller understanding of the reliability of these tests in the first year of life is to be established. Although the early fitting of hearing aids is desirable, the results presented here and those in the literature express the need for caution in using the results measured in the neonatal period. Continuous monitoring of the hearing threshold of any infant failed at birth is obviously essential.

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References

[1] Newton VE. Aetiology of bilateral sensori-neural hearing loss in young children. *J Laryngol Otol* 1985;suppl **10**:40–1.

[2] McCormick B. Hearing screening by health visitors—a critical appraisal of the distraction test. *Health Visitor* 1983;**56**:449–51.

[3] Murray A, Javel E, Watson CS. Prognostic validity of auditory brainstem evoked response screening in newborn infants. *Am J Otolaryngol* 1985;**6**:120–31.

[4] Kemp DT. Stimulated acoustic emissions from within the hearing system. *J Acoust Soc Am* 1978;**64**:1386–91.

[5] Johnsen NJ, Bagi P, Elberling C. Evoked acoustic emission from the human ear. III. Findings in neonates. *Scand Audiol* 1983;**12**:17–24.

[6] Elberling C, Parbo J, Johnsen NJ, Bagi P. Evoked acoustic emission: clinical application. *Acta Otolaryngol (Stockh)* 1985; suppl **421**:77–85.

[7] Stevens JC, Webb HD, Smith MF, Buffin JT, Ruddy H. Comparison of oto-acoustic emissions and brain stem electric response audiometry in the normal newborn and babies admitted to a special care baby unit. *Clin Phys Physiol Meas* 1987;**8**:95–104.

[8] Kemp DT, Bray P, Alexander L, Brown AM. Acoustic emission cochleography-practical aspects. *Scand Audiol [Suppl]* 1986;**25**: 71–95.

[9] Stevens JC, Ip B. Click evoked oto-acoustic emissions in normal and hearing impaired adults. *Br J Audiol* 1988;**22**:45–9.

[10] Rutten WLC. Evoked acoustic emissions from with abnormal human ears: comparison with audiometric and electrocochleographic findings. *Hear Res* 1980;**2**:263–71.

[11] Nield TA, Schrier S, Ramos AD, Platzker AC, Warburton D. Unexpected hearing loss in high-risk infants. *Pediatrics* 1986;**78**: 417–22.

[12] Guerit JM. Applications of surface recorded potentials for the early diagnosis of hearing loss in neonates and premature infants. *Acta Otolaryngol [Suppl] (Stockh)* 1985;**421**:68–76.

[13] Galambos R, Hicks GE, Wilson MJ. The auditor reliably predicts hearing loss in graduates of a tertiary intensive care nursery. *Ear and Hearing* 1984;**5**:254–60.

[14] McCormick B, Curnock DA, Spavins F. Auditory screening of special-care neonates using the auditory response cradle. *Arch Dis Child* 1984;**59**:1168–72.

[15] Duara S, Suter CM, Bessard BS, Gutberlet RL. Neonatal screening with auditory brainstem responses: results of follow up audiometry and risk factor evaluation. *J Pediatr* 1986;**108**: 276–81.

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Increases in plasma concentrations of a prostaglandin metabolite in acute airway obstruction

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SUMMARY Plasma concentrations of a stable prostaglandin F_2 α metabolite were measured by radioimmunoassay during and after recovery from acute airway obstruction in 15 infants. Mean (SEM) metabolite concentrations (ng/l) in plasma obtained both before (1033 (418)) and after (1470 (413)) initial treatment for airway obstruction were significantly higher than those obtained from the same subjects after resolution of the obstruction—25·5 (6·6)—and those obtained from two comparison groups. Infants positive for respiratory syncytial virus (mean 1122 (227)) had significantly higher concentrations than those who were negative (207·6 (46)). Additionally, seven subjects with a history of recurrent wheezing after resolution of airway obstruction had a significantly higher mean level (3500 (1400)) during attacks of airway obstruction than those without (600 (100)). These data suggest that prostaglandin F_2 α mediates respiratory inflammation in airway obstruction and that trials of specific anti-inflammatory agents for the treatment of airway obstruction may be warranted.

Acute airway obstruction is commonly diagnosed in children less than 2 years of age. Potential causes include viral bronchiolitis[1] and asthma, which is subsequently diagnosed in approximately 30–50% of affected infants.[2] Bronchiolitis and asthma share certain signs including wheezing, hyper-reactivity of the airway, and association with viral infections; a common pathogenesis has been postulated for the two syndromes.[3] Recent investigations support the hypothesis that asthma is an inflammatory disease of the lower airways.[4–6] Increased concentrations of various inflammatory mediators in plasma, including histamine and neutrophil chemotactic factor of anaphylaxis, have been reported during acute asthmatic attacks[4] and after bronchial provocation.[5] Welliver *et al* reported increased concentrations of histamine and respiratory syncytial virus-specific IgE antibodies in nasopharyngeal secretions of children with respiratory syncytial virus bronchiolitis, but did not report on plasma histamine concentrations.[7] Measurement of mediators in plasma may be useful as it avoids the dilutional errors common in analysis of nasal washes. Additionally, plasma concentrations might reflect the severity more accurately, as the nasal site is distant from the inflammation in the lower airways.

The purpose of the present study was to determine whether plasma concentrations of a mediator of inflammation with known bronchoconstrictive properties were increased during acute airways obstruction. Specifically, nasal and plasma concentrations of a stable prostaglandin F_2 α metabolite were measured in infants during and after recovery from acute airway obstruction.

Patients and methods

This research was approved by the Children's Hospital Human Experimentation Committee. Informed consent was obtained from the parents of all study subjects.

STUDY DESIGN

The criteria for study entry included age less than 1 year, history of rhinorrhea, cough and fever for no more than 48 hours, and airway obstruction defined as wheezing heard on auscultation of the chest associated with tachypnoea. Children with a previous history of wheezing, allergic or immunological disorders, or heart disease were excluded. Infants who fulfilled the entry criteria were enrolled in the study either after evaluation in the emergency department or following admission to hospital. Infants in the first group (n=9) were studied in the outpatient clinical research centre of the Children's Hospital of Pittsburgh. Indwelling venous catheters were placed in six of these infants to permit collection of venous blood both before and after treatment had been started with nebulised isoetharine. Blood samples were obtained by needle venipuncture from the remaining six subjects, all of whom were studied within 48 hours of onset of symptoms having received nebulised isoetharine before enrolment. In infants with severe respiratory distress or who did not respond to the bronchodilator, arterial blood obtained for blood gas determination was also assayed for the prostaglandin metabolite. Blood was also obtained from two age matched groups for comparison.

Nasal fluids were collected as previously described,[8] cultured for respiratory syncytial virus in HEp2 cells, assayed for respiratory syncytial virus antigen by enzyme linked immunosorbent assay (ELISA) (Ortho Diagnostics),[9] and the remainder stored frozen at −70°C until assayed for prostaglandin metabolite. Nasal fluids from a subset of study subjects (n=7) were assayed for protein concentration using a previously described method.[10] The degree of airways obstruction was estimated clinically using the combination of a scoring system and the respiratory rate at the time of each blood collection.

Of the 15 study patients, 13 returned for re-evaluation and repeat blood studies about six months after the acute attack of airway obstruction. Each parent was asked whether their child experienced any respiratory symptoms after the resolution of the acute attack. Infants in whom a reference of wheezing and tachypnoea had been documented were assigned to the group with recurrent wheezing, while the others were assigned to the group without recurrent wheezing.

CLINICAL SCORE

Each subject was evaluated by one of two investigators (DS: n=13, or HD: n=2). The results of a preliminary study indicated low interobserver variability in the assessment of physical signs associated with lower airways obstruction. Based on results of the examination, each subject was assigned a numerical score from 0 (least severe) to 3 (most severe) for each of the following variables: cyanosis, rib retraction, air entry, inspiratory:expiratory ratio, level of consciousness, and wheezing. The numerical values for each variable were added to yield a total score, which along with resting respiratory rate, was used to estimate severity.

SUBJECTS

Fifteen infants (mean age 3·4 months, range 1–7) were studied. A positive family history of allergies and asthma was present in nine (62%) and 10 (69%) study subjects, respectively. The duration of symptoms before enrolment into the study was two to six hours in one subject, 12–24 hours in six, and 24–48 hours in the remainder. All subjects presented with tachypnoea, ranging from 52 to 84 breaths/minute (mean 64·4). Clinical scores on presentation ranged from 2 to 11 (mean 3·4). Of the nine subjects admitted to hospital, two were premature and required mechanical ventilation for respiratory failure. Either respiratory syncytial virus or respiratory syncytial virus antigen was detected in nasal washings of nine of 14 (64%) subjects. At follow up six months after resolution of the acute airway obstruction, seven of 13 subjects (54%) had a history of recurrent wheezing, and one wheezed on auscultation. This infant returned for a second follow up visit at which time no wheezing was detected.

For comparison, two additional groups of age matched children were studied. These comprised infants who either were normal (n=9, no respiratory infection) or had an upper respiratory infection, pneumonia without wheezing, or fever without obvious cause (n=6).

PROSTAGLANDIN METABOLITE ASSAY

Because the half life of prostaglandin F_2 α in the circulation is only a few minutes,[11] concentrations of one of its stable metabolites, a 13,14-dihydro-15-keto moeity, were measured using a competitive radioimmunoassay as previously described.[4] The rabbit antibody used in this assay (Seragen) displayed the following cross reactivities: prostaglandin F_2 1·7%; 13,14-dihydro-15- keto- prostaglandin E_2 0·14%; 6-keto prostaglandin F_1 0·02%; thromboxane B_2 0·02%; prostaglandin E_2 0·02%; prostaglandin E_1 0·02%; 11-beta prostaglandin F_2 α (Biomol) 0·02%; and prostaglandin F_2 β 0·02% and 15-keto-prostaglandin F_2 β 8·4%. The sensitivity of the assay is 2·7 ng/l and samples with lower concentrations of metabolite are reported as <2·7 ng/l. Plasma prostaglandin metabolite concentrations are expressed as ng/l; concentrations in nasal fluid were analysed as both ng/l and ng/g of protein for normalisation.

DATA ANALYSIS

Samples obtained from study subjects were grouped by collection time, site of collection (artery, vein, nose), respiratory syncytial virus positivity, and recurrence of wheezing. The mean plasma and nasal prostaglandin metabolite concentrations of the groups were calculated and compared. Indicators of severity (respiratory rate and clinical score) and family histories (asthma and allergies) were also correlated with corresponding concentrations of metabolite. Unless otherwise specified, data are presented as mean (SEM) and were analysed by Student's *t* test.[12]

Subjects' blood samples were divided into three groups for analysis: group I—samples collected on presentation to the emergency department before treatment for acute airway obstruction (n=9); group II—samples collected after treatment had been started, but within 48 hours of the onset of symptoms (n=19); and group III—samples collected at the follow up visit, when the infant was free of symptoms (n=13). Normal infants with no respiratory infection (n=9) and infants with upper respiratory infections, pneumonia without wheezing, or fever without obvious cause (n=6) comprised groups IV and V, respectively.

Results

Prostaglandin metabolite values before and after initial treatment and after resolution ranged from 74–3600 ng/l, 13–7240 ng/l, and <2·7–84 ng/l, respectively. Concentrations from both before (1033 (418)) and after (1470 (413)) treatment had been started were significantly higher ($p<0·005$) than those from the same subjects after resolution of symptoms (25·5 (6·6)). The difference between concentrations before and after treatment was not significant and the value after resolution was not significantly different from that of normal infants (42·0 (20·4)), or infants in the comparison group (33·5 (17)). These latter values do not differ from those reported for normal individuals by radioimmunoassay,[13] gas chromatography and mass spectrometry,[14 15] and with the calculated rate of prostaglandin F_2 α synthesis in humans.[15] The plasma prostaglandin metabolite concentration of the single infant in the comparison group (group V) who had pneumonia without wheezing was less than the lowest detectable concentration. To illustrate the group differences, plasma concentrations of the metabolite were converted to log values (fig 1). The mean (SD) log values of groups I to V inclusive were 2·7 (0·53), 2·8 (0·73), 1·19 (0·47), 1·21 (0·64) and 0·6 (1·2), respectively.

Prostaglandin metabolite concentrations in the subgroups of infants who were artificially ventilated or who had intravenous catheters were not significantly different from those in the other study subjects. This suggests that the increases in plasma concentrations were not iatrogenically induced by manoeuvres undertaken in the care of the patients. In support of this hypothesis, intravenous catheters were inserted in three healthy individuals, and did not result in increases in plasma prostaglandin metabolite concentrations 5, 15, and 60 minutes later (unpublished observations).

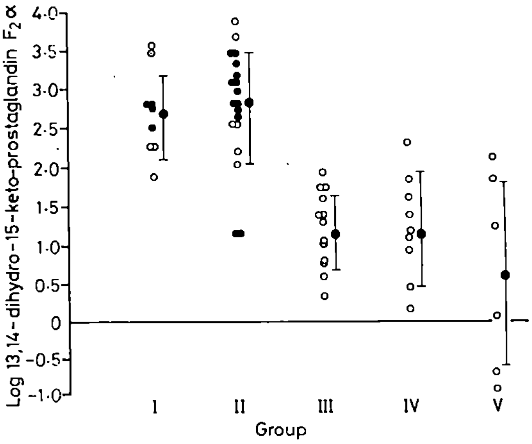

Fig 1 *Log distribution of plasma concentrations of 13, 14-dihydro-15-keto-prostaglandin F_2 α in subjects with airway obstruction (groups I, II, and III) and in comparison subjects (groups IV and V). Vertical lines indicate mean (SD). Closed circles indicate subjects positive for respiratory syncytial virus. Airway obstruction samples are grouped by collection time: group I—before treatment for acute airway obstruction (n=9); group II—after initial treatment, but within 48 hours of onset of symptoms (n=19); and group III—after resolution of acute airway obstruction (n=13). Group IV—normal children (n=9); group V—infants with upper respiratory infection, pneumonia without wheezing or fever without obvious cause (n=6).*

More than one blood sample was obtained from six of the subjects during the study period. As shown in fig 2, three representative subjects had increased, decreased, or unchanged plasma prostaglandin metabolite concentrations after bronchodilator treatment had been started. All values returned to normal at the follow up visit, except the one patient who was wheezing at the six month follow up visit. This patient was not wheezing when evaluated one month later, at which time the concentration had returned to normal (6·2 ng/l).

The concentrations (ng/l) in arterial blood obtained after treatment (1782 (432·9), n=5) were higher than those in venous blood taken after treatment from either the same subjects (952·4 (136·2)) or from the whole group (1470 (413·2), n=19), but these differences were not significant. This arterial venous difference was also observed when simultaneous venous (939·2 ng/l) and arterial (2921 ng/l) samples were obtained from one subject who required artificial ventilation for respiratory failure.

Prostaglandin metabolite concentrations in nasal secretions (n=12) ranged from <2·7 to 1645 ng/l, mean 383·8 (120·6) ng/l. After normalisation with

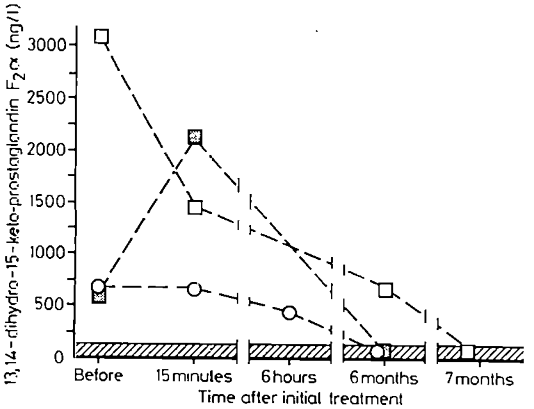

Fig 2 *Patterns of change in plasma 13,14-dihydro-15-keto-prostaglandin F_2 α concentrations (ng/l) before and after initial treatment for acute airway obstruction in three typical infants. Note persistently increased concentration in one infant (open squares) at six month follow up visit when wheezing, then return to normal range at seven month follow up visit when not wheezing. Cross hatched area represents two standard deviations above the mean for normal age matched infants (95% confidence interval).*

protein content, nasal prostaglandin metabolite concentrations ranged from 172 to 8225 ng/g protein, mean 1781 (1088). The increases were often accompanied by similar increases in plasma concentrations, but a significant positive correlation between these two variables could not be shown before or after normalisation (Pearson product moment correlation coefficient).[16]

Plasma and nasal concentrations of prostaglandin metabolite were compared with corresponding indicators of severity (clinical score and respiratory rate) for each subject. Even though both plasma and nasal metabolite concentrations were often considerably raised in the most severely ill infants, a positive correlation could not be demonstrated for any of the clinical variables using the Spearman rank correlation coefficient.[17] Necessity for hospital admission was also used as an indicator of more severely ill infants, and metabolite concentrations in infants in hospital (1147 (656)) were not significantly different from outpatients (1087 (403)).

Nasal and plasma metabolite concentrations during acute attacks of airways obstruction were compared for infants with and without recurrent wheezing after resolution. Concentrations both before and after treatment were higher in the subjects with recurrent wheezing than in those without, but this difference was significant ($p<0·025$) only for the concentrations after treatment (3500 (1400) ng/l compared with 600 (100) ng/l, respectively). Nasal metabolite concentrations were not significantly different between the two groups.

When subjects were grouped according to the presence or absence of respiratory syncytial virus or respiratory syncytial virus antigen in nasal washings, infants positive for respiratory syncytial virus (1122 (226·7) ng/l) had significantly higher plasma metabolite concentrations ($p<0·05$) than those who were negative for respiratory syncytial virus (207·6 (46·2) ng/l) during acute attacks of airway obstruction (fig 1). A significant difference between the two groups could not, however, be shown for nasal concentrations. Even though plasma concentrations were higher in infants with family histories of allergies and asthma (1468 (523) and 1386 (496), respectively) compared with those without such histories (688 (440) and 794 (514), respectively), the differences were not significant. Additionally, metabolite concentrations were not significantly different in infants whose symptoms had lasted 12 to 24 hours (1854 (707)) compared with those whose symptoms had lasted 24 to 48 hours (571 (421)).

Discussion

The results of this study show for the first time that plasma levels of a prostaglandin F_2 α metabolite are considerably increased (fifty fold) in infants with acute airway obstruction, and return to normal after the acute process has resolved. Several pieces of evidence suggest that many of these infants had bronchiolitis, but whether this represented their first episode of asthma is not clear. Lesser increases of the same metabolite were observed during acute asthmatic attacks by our laboratory staff,[4] and during provoked episodes of wheezing and bronchospasm by others.[14] These increases in plasma concentrations probably reflect much higher local concentrations of the metabolite's active precursor molecule, prostaglandin F_2 α, in the tissue of origin. Prostaglandin F_2 α is a potent bronchoconstrictor[18] and secretogogue,[19] the primary synthetic and metabolic site of which is the lung.[13] These observations suggest that prostaglandin F_2 α is a mediator of airway inflammation in airway obstructive disorders.

The likely tissue source for the prostaglandin metabolite is the lung, which is a major site for prostaglandin synthesis by the cyclo-oxygenase pathway of arachidonic acid metabolism, and for release and degradation of prostaglandins.[13] Carrier mediated prostaglandin uptake by lung tissue, followed by cytoplasmic enzyme inactivation and subsequent release of 15-keto and 13,14-dihydro-15-

keto-metabolites[20] has been postulated. Thus metabolites appear in effluent pulmonary venous and systemic arterial blood, capillary vascular beds and then venous plasma. The arteriovenous gradient for the prostaglandin metabolite observed in the present study suggests that a portion of the circulating metabolite is removed or degraded in the capillary microvascular bed.

Both pulmonary macrophages[21] and epithelial cells[22] have been reported to synthesise prostaglandins. Cellular prostaglandin synthesis can be triggered by diverse physiological and pathological stimuli, including viruses. Respiratory syncytial virus and other viral agents could directly or indirectly induce prostaglandin synthesis. A pathogenetic role for IgE dependent hypersensitivity has been postulated in bronchiolitis.[7] A virus specific, type I hypersensitivity reaction with histamine release could result in the direct stimulation of pulmonary prostaglandin synthesis and release in airway obstruction. Alternatively, viruses may stimulate prostaglandin synthesis indirectly. Interferon, a glycoprotein secreted by cells in response to viral infection, is a potent inducer of cellular prostaglandin synthesis and secretion.[23] In support of the hypothesis of a virus induced prostaglandin synthesis, plasma metabolite concentrations were significantly higher ($p<0{\cdot}05$) in infants with respiratory syncytial virus positive airway obstruction when compared with those who were respiratory syncytial virus negative.

In contrast to results reported by Welliver *et al* for histamine,[7] nasal prostaglandin metabolite concentrations did not correlate with two clinical indicators of severity, even after normalisation to protein content. Although the reason for this discrepancy is unclear, several possible explanations should be considered. The nasal mucosa may not synthesise large quantities of prostaglandin F_2 α during airway obstruction or, alternatively, could lack the enzymes necessary for conversion of prostaglandin F_2 α to its stable metabolite. The concentrations measured in nasal fluids could also partly represent plasma exudation of metabolite formed in the lung. A second possible explanation is the variability inherent in the technique of nasal fluid collection. The volume of fluid recovered during washing procedures is variable and could result in inconsistent dilutions and spurious metabolite concentrations. A lack of correlation after normalisation of metabolite to protein concentrations, however, makes this possibility unlikely. Alternatively and even less likely, the indicators used in the present study may lack sufficient sensitivity or specificity in identifying severely ill infants. A similar lack of correlation between clinical severity and plasma metabolite concentrations supports this hypothesis.

Even though the incidence of recurrent wheezing in this study is similar to that reported previously,[2] the follow up period is probably too short to detect all subjects who will ultimately have recurrent wheezing. Indeed, wheezing may not recur until several years after the acute attack of airway obstruction. Further prospective studies of this group are being conducted to clarify this issue. None the less, in the present study, infants who carried on wheezing after resolution of airway obstruction had significantly higher plasma metabolite concentrations during the acute illness than those who did not. This suggests that an increased pulmonary concentration of prostaglandin F_2 α predisposes infants to airway hyper-reactivity and recurrences of wheezing or, alternatively, that a relative hyper-responsiveness of prostaglandin synthesising cells is present in the subgroup of infants who later experience recurrences.

The elaboration of prostaglandin F_2 α and perhaps other bronchoconstrictive mediators of inflammation during acute airway obstruction should provide a stimulus for the development of specific anti-inflammatory agents to supplement bronchodilators in the treatment of infantile airway obstruction.

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References

[1] Henderson FW, Clyde WA, Collier AM, Denny FW. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J Pediatr* 1979;**95**:183–90.

[2] Rooney JC, Williams HE. The relationship between proven viral bronchiolitis and subsequent wheezing. *J Pediatr* 1971;**79**: 744–7.

[3] McIntosh K. Bronchiolitis and asthma: possible common pathogenetic pathways. *J Allergy Clin Immunol* 1976;**57**:595–604.

[4] Skoner DP, Page R, Asman B, Gillen L, Fireman P. Plasma elevations of histamine and a prostaglandin metabolite in acute asthma. *Am Rev Respir Dis* 1988;**137**:1009–14.

[5] Lee TH, Nagakura T, Cromwell O, Brown MJ, Causon R, Kay AB. Neutrophil chemotactic activity and histamine in atopic and nonatopic subjects after exercise-induced asthma. *Am Rev Respir Dis* 1984;**129**:409–12.

[6] DeMonchy JG, Kauffman HF, Venge P, *et al.* Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985;**131**:373–6.

[7] Welliver RC, Wong DT, Sun M, Middleton E, Vaughan RS, Ogra PL. The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. *N Engl J Med* 1981;**305**:841–6.

[8] Hall CB, Douglas RG. Clinically useful method for the isolation of respiratory syncytial virus. *J Infect Dis* 1975;**131**:1–5.

[9] Lauer BA, Masters HA, Wren CG, Levin MJ. Rapid detection of respiratory syncytial virus in nasopharyngeal secretions by enzyme-linked immunosorbent assay (ELISA). *J Clin Microbiol* 1985;**22**:782–5.

[10] Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951;**193**:265–75.

[11] Ferreira SH, Vane JR. Prostaglandins: their disappearance from and release into the circulation. *Nature* 1967;**216**:868–73.

[12] Snedecor GW, Cochran WG. The normal distribution. In: Snedecor GW, Cochran WG, eds. *Statistical methods*. 7th ed. Ames: Iowa State University Press, 1980:54.

[13] Robinson C, Hardy CC, Holgate ST. Pulmonary synthesis, release and metabolism of prostaglandins. *J Allergy Clin Immunol* 1985;**76**:265–71.

[14] Green K, Hedqvist P, Svanborg N. Increased plasma levels of 15-keto-13,14-dihydro-prostaglandin F_2 α after allergen-provoked asthma in man. *Lancet* 1974;**ii**:1419–21.

[15] Samuelsson B, Green K. Endogenous levels of 15-keto-dihydro-prostaglandins in human plasma. *Biochemical Medicine* 1974;**11**: 298–303.

[16] Snedecor GW, Cochran WG. The normal distribution. In: Snedecor GW, Cochran WG, eds. *Statistical methods*. 7th ed. Ames: Iowa State University Press, 1980:175.

[17] Siegel S. *Nonparametric statistics for the behavioural sciences*. Tokyo: McGraw-Hill, Kogakusha, 1956:202–13.

[18] Demers LM. Prostaglandins. In: Race G, ed. *Laboratory medicine*. Hagerstown: Harper and Rowe, 1983:1–21.

[19] Marom Z, Shelhamer JH, Kaliner M. The effects of arachidonic acid derivatives on the release of mucous glycoproteins from human airways. *J Clin Invest* 1981;**67**:1695–1702.

[20] Robinson C, Hoult JRS. Inactivation of prostaglandins in the perfused rat lung. *Biochem Pharmacol* 1982;**31**:633–8.

[21] Kouzan S, Brody AR, Nettesheim P, Eling T. Production of arachidonic acid metabolites by macrophages exposed *in vitro* to asbestos, carbonyl iron particles, or calcium ionophore. *Am Rev Respir Dis* 1985;**131**:624–32.

[22] Xu Gl, Sivarajah K, Wu R, Nettesheim P, Eling T. Biosynthesis of prostaglandins by isolated and cultured airway epithelial cells. *Exp Lung Res* 1986;**10**:101–14.

[23] Fitzpatrick FA, Stringfellow DA. Virus and interferon effects on cellular prostaglandin biosynthesis. *J Immunol* 1980;**125**:431–7.

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Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma

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SUMMARY A new self administered questionnaire completed by parents was used to study the prevalences of wheeze, shortness of breath, and cough in 2503 Southampton schoolchildren aged 7 and 11 together with exacerbating factors and background information including treatment and diagnosis. The questionnaire had a response rate of 84% and was found to be highly repeatable with respect to current symptoms. The overall prevalences of wheeze and shortness of breath in the current year (1986) were 12·1% and 8·5% respectively. Social class, home ownership, parental smoking, and presence of a family pet were unrelated to symptom prevalence. According to the parents the overall diagnosis rate for asthma was 9·5%. In common with other studies, however, we found considerable evidence for undertreatment. The symptoms of wheeze and nocturnal and morning breathlessness occurred more commonly in boys, but this sex ratio decreased with increasing age. The prevalences of wheeze and shortness of breath were similar in the two age groups. In contrast, there were only small differences between the sexes with respect to cough whereas, among children without wheeze or shortness of breath, there was a fall in the prevalence of cough from 18·9% at 7 years to 8·7% at 11 years. When controlling for the other respiratory symptoms, wheeze was the only symptom significantly related to parental asthma. The fall in the prevalence of cough between the two age groups is unlikely to be related to changes in asthma prevalence and, when not associated with wheeze, may be an indicator of separate pathology.

Studies of the prevelance of asthma produce widely varying rates even among European populations.[1] These differences may be largely explained in terms of varying definitions of asthma and undue reliance on general practitioner diagnoses. This is confirmed by the considerably greater concordance between studies with respect to particular respiratory symptoms. Reliable information can only be gained if wheeze has been defined and explained adequately to parents.[2–4] In a cross section survey in Melbourne, Williams and McNicol recorded a cumulative prevalence of 19% for wheeze at 7 years.[2] Anderson *et al* reported a prevalence of 11% for wheeze during the current year in 9 year olds in Croydon.[3] Lee *et al* found a prevalence of 14·8% between school entry and 7 years in northern England and showed reasonable concordance between a questionnaire history of wheeze and a clinical diagnosis of asthma defined by 'episodic airways obstruction characterised by wheeze or breathlessness'.[4] Using a similar definition, the prevalence of asthma in 470 London children aged between 18 months and 11 years was found to be 11%.[5]

Although epidemiological studies on the prevalence of wheeze avoid difficulties over the definition of asthma, the possibility arises that the symptom of wheeze may occur in disorders other than classical asthma. In childhood asthma, other symptoms, particularly cough and breathlessness are also known to be important. There have been a number of reports of cough being the sole presenting symptom of asthma,[6–9] however, the prevalence of this and other respiratory symptoms in childhood and their importance in the absence of wheeze has not been well studied.

A number of factors are known to affect the prevalence of asthma or the symptom of recurrent wheezing during childhood. The tendency for the symptoms to improve with age is well known,[10 11] although longer term follow up shows later recurrence.[12–14] Boys have a higher prevalence of asthma in childhood but this difference disappears in adults and may be reversed in some age groups.[15] Asthma is said to be diagnosed more commonly in the upper social groupings and home owner occupiers.[16] Fathers are less likely than mothers to admit to symptoms in their children.[17] A variety of factors have also been implicated in the pathogenesis of episodic wheezing and asthma and include inheritance,[18–20] viral infection,[21–23] exposure to common allergens,[24 25] and parental smoking.[26 27] In this study we have used a new questionnaire developed to explore the prevalence of common respiratory symptoms in schoolchildren and their association to each other, the diagnosis of asthma, and genetic and environmental factors.

Subjects and methods

SUBJECTS

All children in their third year at 55 Southampton first and middle schools were studied by parental questionnaire over a six week period during the second half of the school summer term. The standardised movement of children between classes conveniently divided the children into two almost exact one year age ranges: 6·8 to 7·8 years in first schools and 10·8 to 11·8 years in middle schools. The schools comprised 30 of the 40 first schools in Southampton, 18 of the 28 middle schools, and seven of the 10 combined first and middle schools. Altogether questionnaires were sent to the parents of 2981 children. Questionnaires were delivered to the schools and given to the children to take home and they, in turn, returned them to the school when they had been completed. The local education authority would not allow release of names and addresses of children by the schools, thus although it was possible to calculate return rates, we were unable to obtain comparative information on children not returning questionnaires.

QUESTIONNAIRE DESIGN

In view of the lack of a complete and well validated respiratory questionnaire for use in children suitable for a study of asthma, a new questionnaire was designed. The project demanded a self administered questionnaire that was simple to complete by parents and likely to result in high compliance. The length of the questionnaire was limited to six sides of 'A4' paper.

Wheeze and dyspnoea were identified by the questions: 'Has your child ever had an attack of wheezing (by wheezing I mean noisy breathing with a whistling sound coming from the chest not the throat)?' and 'Has your child ever been either unexpectedly breathless at rest or more breathless than you would expect after exercise (by breathless I mean out of breath or puffed)'. Three questions were used to identify abnormal cough. Parents were asked 'Has your child ever seemed to cough more (or to get more coughs) compared to other children'. Two further questions were designed to identify recurrent coughing, unrelated to upper respiratory tract infection, occurring at night or first thing in the morning. Symptoms within the previous 12 months were classified as current and as past if occurring >12 months before completion of the questionnaire.

Further information characterising the current symptoms was obtained using questions aimed at identifying exacerbating factors. Information was further sought on chest pain or discomfort which has been described as a presenting symptom of asthma.[5] Morbidity was briefly assessed using two questions —one on hospital admission and the other on number of days of school lost during the past year. The last part of the questionnaire provided background information on the children. Medical diagnoses given to the parents relating to the child's chest problem were sought together with any current medications being used. Questions on parental smoking habits, household pets, and parental asthma were also included. Social status was defined by enquiry of each parent's occupation and the family's accommodation whether rented or owner occupied.

REPEATABILITY AND VALIDITY TESTING

The repeatability of the questionnaire was tested by readministration to 200 parents. Children were selected with an increased preponderance of positive answers to the key questions on wheeze, cough, and shortness of breath: 50 cases denied all symptoms, 50 had wheeze alone, 31 shortness of breath alone, and 69 both shortness of breath and wheeze (the odd numbers in the last two groups resulted from the small numbers in the shortness of breath only group). Parents were only asked to fill in the sections on respiratory symptoms to improve compliance. The questionnaire was readministered four months after the original questionnaire in an attempt to avoid deliberate mimicking of previous answers but making a major change in symptom incidence or severity unlikely.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences edition X was used for categorisation and analysis of data.[28] Correlations between variables were calculated using the χ^2 test or, when controlling for other variables, the Mantel-Haenszel test. Repeatability of questionnaire replies was calculated both in terms of percentage agreement and by calculation of κ, which is an index of repeatability described by Cohen,[30] calculated by the formula: $P_O - P_C/1 - P_C$ where P_O represents the proportion of agreement for the question and P_C is the proportion of agreement expected by chance. It is thus independent of chance agreement so that comparison can be made between questions with differing proportions of positive and negative replies.

Table 1 *Repeatability of questions relating to current symptoms, school loss, and hospital admission*

Questions	*% Agreement*	κ
Wheeze current 12 months?	88·9	0·78
Woken by wheeze?	81·6	0·53
Wheeze in the morning?	88·0	0·69
Breathless current 12 months?	78·1	0·50
Woken by breathlessness?	88·9	0·42
Breathless in the morning?	87·0	0·37
Coughs more than others?	80·0	0·57
Night time cough?	83·0	0·60
Morning cough?	75·0	0·47
School loss?	88·4	0·73
Admitted to hospital?	95·8	0·79
Ever chest pain/discomfort?	76·3	0·47
Sleep loss due to chestiness?	84·2	0·67

Results

RESPONSE RATES AND REPEATABILITY

A total of 2503 replies were received from the 2981 questionnaires sent, representing an overall response rate of 84%. The response rates in the two age groups were similar with 1275 replies from the parents of the 7 year olds and 1218 from the 11 year old group. There were slightly more boys than girls in both age groups with a male:female ratio of 1·03:1. The response rates at different schools varied widely but there was less association with the range of social classes surrounding the school than with the quality of the relationship between the school and the parents. One school in a 'problem area' achieved a questionnaire return rate of 100%. The return rate for the readministered questionnaire was lower at 50% of the 200 questionnaires sent out. The social class range of the responders to the repeat questionnaire was compared with that of the responders to the first administration but no significant differences could be shown.

The results of the repeatability study are presented in table 1. The questions on wheeze were the most

Table 2 *Prevalences of individual symptoms by age and sex. Results are given as a percentage with that symptom of the number of children whose parents replied to the relevant question in the questionnaire*

Symptoms	*Age 7 years*		*Age 11 years*	
	Girls *% (No)*	*Boys* *% (No)*	*Girls* *% (No)*	*Boys* *% (No)*
Wheeze:				
Cumulative***	15·9 (623)	22·7 (651)	16·7 (604)	19·9 (613)
Current 12 months***	9·5 (621)	14·3 (651)	10·9 (604)	13·7 (613)
Nocturnal	6·3 (622)	7·9 (648)	6·6 (603)	9·1 (613)
Morning***	3·5 (621)	8·9 (650)	7·3 (603)	8·0 (612)
Shortness of breath:				
Cumulative†*	7·2 (621)	12·3 (649)	13·4 (598)	13·6 (611)
Current 12 months	4·8 (620)	9·0 (647)	10·3 (592)	10·0 (607)
Nocturnal***	1·9 (620)	5·2 (649)	3·9 (597)	4·9 (609)
Morning***	1·6 (619)	4·3 (648)	2·5 (596)	4·1 (608)
Cough				
Current 12 months‡*	27·9 (623)	33·7 (603)	19·3 (519)	22·2 (554)
Nocturnal‡	17·3 (573)	18·2 (605)	8·7 (530)	12·4 (565)
Morning‡	18·5 (567)	22·6 (606)	13·0 (530)	13·8 (560)
Chest discomfort‡*	7·9 (595)	13·0 (630)	14·2 (593)	15·1 (597)
'Chesty' at night‡	18·2 (598)	20·3 (636)	12·4 (588)	14·6 (597)
Hospitalised with wheeze and/or shortness of breath:				
Cumulative†*	4·5 (594)	6·9 (622)	3·0 (569)	4·8 (578)
Current 12 months	4·5 (594)	5·0 (622)	2·8 (569)	3·6 (578)
Medical diagnosis of:				
Asthma***	7·2 (613)	11·7 (642)	8·4 (598)	10·7 (598)
Bronchitis*	11·1 (606)	14·0 (636)	12·4 (597)	14·8 (596)

χ^2 analyses: *p<0·05, ***p<0·001 for girls *v* boys, ignoring age; †p<0·05, ‡p<0·001 for 7 year olds *v* 11 year olds, ignoring sex.

repeatable of the symptom questions. Also highly repeatable were the answers to the enquiry about hospital admissions. Low values of κ were produced for enquiries regarding specific information about symptoms such as when they occurred, and for the symptom of chest pain.

PREVALENCE DATA

The prevalences of individual symptoms are displayed by sex and age in table 2. The cumulative prevalences of wheeze and shortness of breath and the prevalences of diagnosed asthma and bronchitis refer to symptoms since birth. All other symptom categories refer to symptoms within the 12 months preceding receipt of the questionnaire. The current prevalences of wheeze, shortness of breath, and cough among the whole population sample were respectively 12·1%, 11·6%, and 26·8%. The major differences between the sexes appeared to be in the symptoms of wheeze and shortness of breath, in that there were higher prevalences in boys. The label 'asthma' had also been given 1·4 times more frequently in boys than in girls. In contrast, cough appeared to have little relation to gender but showed a considerable and highly significant decrease in prevalence between the ages of 7 and 11 years. Among children without wheeze or shortness of breath, the prevalence of a positive answer to one of the three cough questions fell from 18·9% at 7 years to 8·7% at 11 years. The associations between each of the three symptoms were found to be highly significant ($p<0\cdot001$ for each association controlling for the remaining symptom by the Mantel-Haenszel test).

The higher prevalences of wheeze and shortness of breath in boys are reflected in the higher proportion who had been admitted to hospital both in the current year and since birth with these symptoms. Nearly 5% of the whole group and 7% of 7 year old boys had been admitted to hospital with wheeze or shortness of breath. The higher prevalence of nocturnal 'chestiness' among 7 year olds, compared with 11 year olds, was highly significant ($p<0\cdot001$) and may reflect the higher prevalence of nocturnal cough. The increase in chest pain or discomfort between 7 and 11 years is also significant, but only occurred in girls and thus is unlikely to be related to the other respiratory symptoms.

Analysis of the responses to questions on when respiratory symptoms first occurred, whether they were current, and when they last occurred was used to calculate prevalences for wheeze at each age from birth onwards. These calculated prevalences are likely to be inaccurate due to recall bias and are, therefore, not presented here. Because the degree of bias is likely to be similar between the two sexes, however, we could make observations on the differences between the sexes at different ages. The prevalence of wheeze in boys rose sharply to the age of 5 years with a slight fall off thereafter. In girls the prevalence of wheeze was lower at all ages but the rise in prevalence appeared to continue up to the age of 8 years. The ratio of the prevalence of wheeze in boys to that in girls showed a considerable, and highly significant, decrease with increasing age of the child (figure).

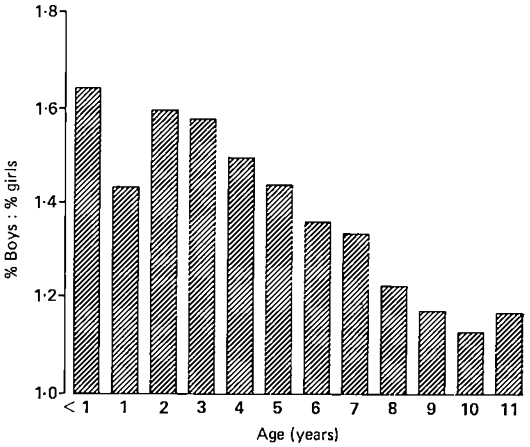

Fig 1 *The ratio of the prevalence of wheeze in boys to that in girls between 0 and 11 years.*

ASSOCIATIONS BETWEEN BACKGROUND DATA AND RESPIRATORY SYMPTOMS

The predominant occupation of parents among those sampled was skilled workers (45%). Sixty six percent were home owners. More than half of the children (56%) were exposed to passive smoking at home. Two thirds of families possessed a pet, this being a cat or dog in 51% of families. However, this study did not show associations between class, passive smoking, or pet ownership and any respiratory symptom. Only age, gender, and the presence of parental asthma showed significant associations with the prevalences of cough, wheeze, and shortness of breath. Parental asthma was positively associated with all three symptoms. Because of the strong associations between each of these symptoms, the Mantel-Haenszel test was used to examine the association between parental asthma and each symptom controlling for the other two. Wheeze remained highly associated with parental asthma ($p=0\cdot0012$) when controlling for cough and shortness of breath, but neither cough nor shortness of breath were significantly associated with parental asthma when controlling for wheeze ($p=0\cdot4$, $p=0\cdot2$ respectively). In addition, no association with the more

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Table 3 *Treatment received by 299 children with current wheeze and 178 with diagnosed asthma in association with either current wheeze or shortness of breath*

Drug treatment	*% With current wheeze*	*% With diagnosed asthma plus symptoms‡§*
No treatment	45·8	19·7 (8·8)
Non-asthma	8·7	5·6 (0)
Inhaled bronchodilator	18·4	31·5 (18·2)
Prophylactic alone*	4·7	8·4 (26·7)
Prophylactic with inhaled bronchodilator	13·4	23·0 (17·1)
Oral bronchodilator†	4·7	5·1 (11·1)
Other drug regime	4·3	6·7 (8·3)

*Inhaled steroids and/or sodium cromoglycate.

†Oral β_2 agonist and/or methylxanthine.

‡Either wheeze or shortness of breath during the previous 12 months.

§Figures in parenthesis refer to 26 children missing >20 days school per year.

'specific' symptoms of nocturnal or morning breathlessness could be shown.

Highly significant associations were observed between symptom prevalences and the sex of the parent completing the questionnaire. The impression was gained during the second part of the study that the father was less likely to complete the questionnaire if the parents perceived illness in the child. No data were collected, however, which would measure the relative importance of this possibility or the possibility that under reporting of symptoms by fathers was occurring.

TREATMENT

The prevalence of 'asthma' as a diagnosis given to the parents was 9·5%. The types of treatment received by the children are listed in table 3. One third of children with current wheeze or shortness of breath who had a diagnosis of asthma were using an inhaled bronchodilator alone, one third were taking prophylactic medication with or without bronchodilators, and one third were on other regimes or receiving no specific treatment. One in five children with cough were receiving medication appropriate for treating asthma, of whom nine had cough as their only symptom; the remainder had cough in association with wheeze or shortness of breath, or both.

Discussion

Epidemiological studies of childhood asthma have increasingly concentrated upon the prevalence of wheeze mainly as a result of difficulties over definition and underdiagnosis of the condition.[31 32] Recent studies have included other symptoms, such as nocturnal cough, but little is known about their epidemiological validity as independent markers of asthma. We have designed and tested a childhood respiratory questionnaire for completion by parents and have used it for measuring the prevalences and inter-relationships of wheeze, shortness of breath, and cough among over 2500 children of 7 and 11 years. The associations of genetic and environmental factors to each of these symptoms have been examined. We have also presented information on morbidity, diagnosis, and treatment received by the children.

The 84% return rate for this questionnaire, containing 33 questions, compares favourably with a 74% return achieved by Mortagy *et al*, also in Southampton, using an adult respiratory questionnaire containing 21 questions.[34] Salome *et al* reported a return rate of 85% for a self administered respiratory questionnaire used in a study of children in 25 schools in two Australian towns using similar collection and delivery methods to the present study.[33] A remarkably high return rate of >99% was reported by Lee *et al* for a questionnaire containing just four questions.[4] Apart from their greater lengths, the questionnaires used by Salome *et al*[33] and ourselves contained some 'sensitive' questions concerning occupation and housing and included a request for consent to be contacted for further study. Because of the high number of schools involved in the present study, a low return from one or two schools with appreciable effects on the overall rate was almost inevitable.

Two questions used in the present study, those for wheeze and night time cough, were similar in wording to questions used by Salome *et al* and had similar repeatabilities in the two studies both in terms of percentage agreement and coefficient of agreement (κ).[33] This indicates that these indices are appropriate for comparisons of repeatability, and has the advantage of being independent of chance agreement which alters with the proportion of positive replies.[30] We found that questions on wheeze were the most repeatable and those on shortness of breath and chest discomfort least repeatable with the cough questions being intermediate. We also recorded high levels of repeatability for questions on school loss and hospital admission.

We have confirmed a lower prevalence of respiratory symptoms when the questionnaire was completed by the father.[17] It is possible that fathers were less likely to fill in the questionnaire in the case of illness in the child because of their smaller role as carers.

Certainly symptoms were most prevalent in children where both parents had completed the questionnaire in conjunction, presumably reflecting increased parental involvement and concern. This impression appeared to be confirmed during the second phase of the study where one of us had the opportunity to meet a large number of the parents.[35 36] The design of the study, however, did not enable us to measure the extent to which under reporting of symptoms by fathers may have been occurring. Fortunately only 9% of questionnaires were completed by the father alone. Clearly, this problem is likely to be common to all such epidemiological studies, including adult studies where males could under report their own symptoms. The sex of the responder to the questionnaire was not related to other factors such as sex or age of the child and, therefore, is not likely to represent a confounding influence upon the associations between these factors and respiratory symptoms.

The prevalence of wheeze in the year preceding the questionnaire (current prevalence) was found to be 12·1% and the cumulative prevalence from birth was 18·8%. These figures are comparable with those reported from other studies in western countries when a similar questionnaire format was used.[2–4] However, there are little published data on the prevalence of other respiratory symptoms in childhood. Shortness of breath, although not occurring as frequently as wheeze, is a common complaint as indicated by a current prevalence of 8·5%. Approximately one third of parents of 7 year old children and one quarter of all parents believed that their children coughed more than others. Nocturnal cough occurred in 14·2% of the total childhood population studied and reached as high as 18·2% in 7 year old boys; however, only half of children with recurrent cough had associated wheeze.

In this study we have confirmed previous observations of a higher prevalence of wheeze in boys when compared with girls. Overall 1·37 times more boys had wheezed during the current year. These differences were reflected in the higher prevalence of shortness of breath among boys compared with girls with the greatest differences occurring in the prevalences of shortness of breath at night and in the early morning. In contrast the differences between the sexes with respect to cough were small and only just reached significance for the current 12 months with insignificant differences for nocturnal cough. Variations in symptom prevalence between the two age groups were also recorded but differed from those occurring between sexes in that they related only to the symptom of cough. A 30% decrease in the prevalence of problematic cough occurred between 7 years and 11 years, which was not accompanied by a change in the prevalence of wheeze. Indeed the most dramatic fall in cough prevalence from 18·9% at 7 years to 8·7% at 11 years occurred in children without associated wheeze or shortness of breath.

Calculation of annual prevalences of wheeze by gender revealed differences between boys and girls. Boys reached their peak prevalence of wheeze by 5 years, but in girls a gradual increase in prevalence continued up to the age of 8 years resulting in a progressive and highly significant decrease in the male to female ratio for wheeze with increasing age (figure). These trends in prevalence and male to female ratio are in line with data published from national morbidity statistics relating to asthma in general practice,[15] and therefore would be worthy of further prospective study.

The presence of asthma in one or more of the parents had appreciable effects on the prevalence of respiratory symptoms in their children. Both wheeze and shortness of breath were reported twice as frequently and cough was 1·4 times more prevalent in this group of children. Although shortness of breath and cough were related to the presence of parental asthma, the association disappeared when we controlled for the symptom of wheeze. In contrast, wheeze remained strongly related to parental asthma even when controlling for both cough and shortness of breath. Assuming that parental asthma is responsible for an increased prevalence of asthma and no other illness in the offspring, wheeze must be a key symptom of asthma with cough and shortness of breath being related but subordinate symptoms. The latter finding, the small male to female ratio in prevalence of cough, and the fall in cough prevalence between the ages of 7 and 11 years with no associated drop in the prevalence of wheeze all point to recurrent cough being of low specificity as an epidemiological marker for asthma.

We were unable to show an association between wheeze or other respiratory symptoms and home ownership or parent's occupation. The assocation between respiratory symptoms and parental smoking reported by Bland *et al* was found from a questionnaire filled in by the children themselves.[26] The absence of an association in our parental questionnaire may represent a degree of denial or lower expectations among parents who smoke. The repeated personal interviews and examinations in the study of Cogswell *et al* may well have avoided this problem.[27] It is reassuring that the prevalence of wheeze was no greater among the two thirds of children with a feathered or furry pet despite the clear importance of animal danders as precipitants of attacks in those with pre-existing asthma.

A remarkable number of children were reported by their parents to have been in hospital with asthma. This is likely to have been reliably reported in view of the importance of such a life event and the good repeatability of this question. The observation that fewer 11 than 7 year olds were admitted to hospital, however, might suggest that parents may have failed to recollect some admissions. The rates for the current 12 months are nevertheless likely to be accurate. Altogether 115 of the children had been admitted to hospital with wheezing or breathlessness comprising 4·9% of the sample including 4% during the previous 12 months. It would seem unlikely that more than a small proportion of admissions could be accounted for by other causes of breathlessness such as acute pneumonia. Anderson *et al* reported a 167% rise in hospital admissions for asthma between 1970 and 1978,[37] and it is likely that this trend has continued with improved awareness of the illness.

The proportion of children (9·5%) whose parents had been told they had asthma was only slightly lower than the 12·1% current prevalence of wheeze. These figures compared with just one eighth of the 9·3% of children identified as having current wheeze who had received a diagnosis of asthma in the study of Lee *et al* in north Tyneside.[4] Our diagnosis rate also compares favourably with the 7·8% reported by Heijne den Bak in a training practice in west Cumbria.[38] Levy and Bell reported a diagnosis rate of 11% but in a practice with a special interest in asthma.[5] The proportion of middle class parents and home owners in this study was high in comparison with the likely range in some inner city environments. Presumably these parents would have higher expectations for accurate diagnosis and effective treatment of their children if they were having disabling symptoms. Despite the apparently excellent diagnosis rate, we found evidence for considerable under treatment of asthma symptoms, as reported in other studies.[31] [32] Fewer than half of children with current wheeze were receiving any appropriate treatment. When the children who had received a diagnosis of asthma and had experienced shortness of breath or wheeze during the current year were analysed, more than a quarter were not receiving any form of antiasthma treatment. Fifteen percent of the children with diagnosed symptomatic asthma were missing more than 20 days of schooling each year, and less than half of these were receiving a prophylactic medication with 9% not receiving any treatment at all.

In conclusion we have developed and tested a new questionnaire for examining the prevalence of respiratory symptoms in children. When applied to a large population of 7 and 11 year old schoolchildren the symptom of wheeze most closely paralleled the diagnosis of asthma with respect to male:female ratio and association to parental asthma. Moreover the high prevalence of cough with or without wheezing and an appreciable decrease of this symptom by the age of 11 years identifies a major respiratory problem in schoolchildren, which is not closely associated with asthma but rather is probably associated with recurrent viral infections and later acquisition of immunity. The study showed strong evidence for under treatment of asthma despite a high diagnosis rate.

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References

[1] Gregg I. Epidemiological aspects. In: Clark T, Godfrey S, eds. *Asthma*. 2nd ed. London: Chapman and Hall, 1983; 242–78.

[2] Williams H, McNicol KN. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J* 1969;**iv**:321–5.

[3] Anderson HR, Bailey PA, Cooper JS, Palmer JC, West S. Medical care of asthma and wheezing illness in children: a community survey. *J Epidemiol Community Health* 1983;**37**: 180–6.

[4] Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;**286**:1256–8.

[5] Levy M, Bell L. General practice audit of asthma in childhood. *Br Med J* 1984;**289**:1115–6.

[6] Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperreactivity. *Pediatrics* 1981;**67**: 6–12.

[7] Konig P. Hidden asthma in childhood. *Am J Dis Child* 1981;**135**:1053–5.

[8] Yahav Y, Katznelon D, Shlomo B. Persistent cough—a forme fruste of asthma. *Eur J Respir Dis* 1982;**63**:43–6.

[9] Hannaway PJ, Hopper GDK. Cough variant asthma in children. *JAMA* 1982;**247**:206–8.

[10] McNichol KN, Williams HE. Spectrum of asthma in children: 1. Clinical and physiological components. *Br Med J* 1973;**iv**:7–11.

[11] Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. *Br Med J* 1980;**280**: 1397–400.

[12] Blair H. Natural history of childhood asthma: 20 year follow up. *Arch Dis Child* 1977;**52**:613–9.

[13] Britten N, Davies J, Colley J. Early respiratory experience and subsequent cough and peak expiratory flow rate in 36 year old men and women. *Br Med J* 1987;**294**:1317–20.

[14] Kelly WJW, Hudson I, Phelan PD, Pain MLF, Olinsky A. Childhood asthma in adult life: a further study at 28 years of age. *Br Med J* 1987;**294**:1059–62.

[15] Fleming DM, Crombie DL. Prevalence of asthma and hay fever in England and Wales. *Br Med J* 1987;**294**:279–83.

[16] Anderson HR, Bailey PA, Cooper JS, Palmer JC, West S. Morbidity and school absence caused by asthma and wheezing illness. *Arch Dis Child* 1983;**58**:777–84.

[17] Schecker MB, Samet JM, Speizer FE. Risk factors for childhood respiratory disease: the effect of host factors and home environment. *Am Rev Respir Dis* 1983;**128**:1038–43.

[18] Edfors-Lubs M. Allergy in 7000 twin pairs. *Acta Allergolica* 1971;**26**:249–85.

[19] Sibbald B, Horn MEC, Brain EA, Gregg I. Genetic factors in childhood asthma. *Thorax* 1980;**35**:671–4.

[20] Clifford RD, Pugsley A, Radford M, Holgate ST. Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children. *Arch Dis Child* 1987;**62**:66–73.

[21] Rooney JC, Williams HE. The relationship between proved viral bronchiolitis and subsequent wheezing. *J Pediatr* 1971;**79:** 744–7.

[22] Sims DG, Gardner PS, Weightman D, Turner MW, Soothill JF. Study of 8 year old children with a history of respiratory syncitial virus bronchiolitis in infancy. *Br Med J* 1978;**i:**11–4.

[23] Horn MEC, Brain EA, Gregg I, Inglis JM, Yealland SY, Taylor P. Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979;**34:**23–8.

[24] Cockcroft DW, Ruffin R, Dolovich J, Hargreave FE. Allergen induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977;**7:**503–13.

[25] Platts-Mills TA, Tovey ER, Mitchell EB, Mozarro H, Nock P, Williams S. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982;**ii:**675–8.

[26] Bland M, Bewley BR, Pollard V, Banks MH. Effect of children's and parent's smoking on respiratory symptoms. *Arch Dis Child* 1978;**53:**100–5.

[27] Cogswell JJ, Mitchell EB, Alexander J. Parental smoking, breast feeding, and respiratory infection in development of allergic diseases. *Arch Dis Child* 1987;**62:**338–44.

[28] *SPSSx users guide.* 2nd ed. New York: McGraw-Hill 1986.

[29] Snecdor GW, Cochran WG. *Statistical methods.* 6th ed. Iowa: Iowa State University Press, 1967:255–6.

[30] Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* 1960;**20:**37–46.

[31] Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *Br Med J* 1983;**286:**1253–6.

[32] Anderson HR, Bailey PA, Cooper JS. Influence of morbidity, illness label and social, family and health service factors on drug treatment of childhood asthma. *Lancet* 1981;**ii:**1030–2.

[33] Salome CM, Peat JK; Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren—I. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;**17:**271–81.

[34] Mortagy AK, Howell JB, Waters WE. Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma. *Br Med J* 1986;**293:**525–9.

[35] Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren. *Arch Dis Child* 1989;**64:**1126–32.

[36] Clifford RD, Howell JB, Radford M, Holgate ST. Associations between respiratory symptoms, bronchial response to methacholine and atopy in two age groups of schoolchildren. *Arch Dis Child* 1989;**64:**1133–9.

[37] Anderson HR, Bailey P, West S. Trends in the hospital care of acute childhood asthma 1970–8: a regional study. *Br Med J* 1980;**281:**1191–4.

[38] Heijne den Bak J. Prevalence and management of asthma in children under 16 in one practice. *Br Med J* 1986;**292:**175–6.

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Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren

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SUMMARY A sample of 397 from 2503 children aged 7 and 11 years, who took part in an earlier questionnaire study of respiratory symptoms in Southampton, was chosen for methacholine bronchial provocation and allergen skin testing. Results were obtained from 330 (84%). A good level of repeatability was achieved for bronchial provocation testing giving a 95% confidence interval equivalent to 1·74 doubling concentrations. The main problem encountered with methacholine was its bitter taste in high concentrations. The proportion of children, in whom the dose of methacholine which produced a fall of 20% in the forced expiratory volume in one second (PD_{20} methacholine) was ≤6·4 μmol, fell from 29·1% at 7 years to 16·5% at 11 years. The prevalence of atopy increased from 26% at 7 years to 31·6% at 11 years. A highly significant association was found between bronchial responsiveness to methacholine and atopy, which was independent of symptoms or age group.

Tests for quantifying non-specific bronchial responsiveness have become commonplace in laboratory based research on asthma. In recent years both histamine and methacholine challenge tests have been introduced for use in community surveys in an attempt to enhance the specificity of questionnaire studies of asthma because of difficulties in the symptomatic definition of this group of diseases. A fixed dose methodology suitable for epidemiological use has recently been described and validated by Yan *et al* and shown to be safe, easy to perform, and highly reproducible in adults.[1 2] The same group have recently reported the use of the method in an epidemiological study of Australian schoolchildren.

In adults Mortagy *et al* have described a collection of symptoms associated with a defined degree of bronchial responsiveness to histamine.[3] It is likely that a significant proportion of asthmatic individuals may fail to show bronchial hyper-responsiveness on a single measurement, a phenomenon that appears to be particularly common in children.[4 5] It is unclear how many individuals may have measurable hyper-responsiveness without symptoms as studies purporting to show this have failed to enquire about all respiratory symptoms and in particular cough, or have failed to separate the latter symptom in their analyses.

Other studies have shown an association between bronchial responsiveness and atopy and indicating a causal interaction.[6–9] The precise role of these two measurements, however, in the aetiology and symptomatic definition of asthma and other respiratory complaints remains a subject of speculation. In this study we have examined the range of bronchial responsiveness and atopy among children randomly selected from a variety of respiratory symptom groups. Moreover, we have endeavoured to optimise the precision of the methodology of Yan *et al* for testing non-specific bronchial responsiveness in children,[1] and have measured its repeatability and comparability with another commonly used method.

Subject and methods

SUBJECTS

The questionnaire part of the study was undertaken in the summer term in 55 schools among 2981 third year first and middle school children between 6·8 and 7·8 years and 10·8 and 11·8 years respectively. The questionnaire used has been described previously.[10]

Children were divided into seven symptom groups according to answers given on the questionnaire (table 1). Each symptom group except group 7 referred to symptoms within 12 months from delivery of the questionnaire. Children in group 2 (cough) did not have wheeze or shortness of breath. Parents of children in group 6 (bronchial irritability)

Table 1 *Distribution of symptoms in the general population, numbers of children invited for testing, and numbers finally tested for atopy and bronchial responsiveness to methacholine*

Symptom group	*Population No (%)**	*No invited for testing*	*No tested for bronchial responsiveness to methacholine*	*No tested for atopy*
1 None	1063 (47·4)	109	80	81
2 Cough alone	348 (15·5)	66	55	54
3 Wheeze with or without cough	142 (6·3)	58	51	51
4 Shortness of breath with or without cough	61 (2·7)	26	24	24
5 Wheeze and shortness of breath with or without cough	150 (6·7)	60	57	57
6 Bronchial irritability†	445 (19·8)	68	54	56
7 Past wheeze/shortness of breath	34 (1·5)	10	9	9
8 Incomplete information	260			

*No of questionnaire replies classified to each symptom group also represented in parentheses as a percentage of the children on which complete information is available.
†See text for explanation of symptom group.

had answered negatively to the cough, wheeze, and shortness of breath sections, although admitting to one or more of these symptoms in response to environmental provoking agents including cold air, fumes, smoke, and exercise. Children were only placed into group 7 (past wheeze/shortness of breath) if they did not fall into any of the current symptom groups (2–6). Symptom groups were thus mutually exclusive. Children in the wheeze and shortness of breath sections invariably also had cough and bronchial irritability as additional symptoms.

From 1 October until the end of the autumn term 1985, 20 visits were made to first schools and 20 to middle schools each providing 10 appointments for testing of atopic status and non-specific bronchial responsiveness. Schools were chosen according to the headteacher's assessment of the appropriateness of facilities comprising 27 of the 55 schools involved in the questionnaire study. One hundred children in group 1 were originally selected together with all children from groups 3, 4, 5, and 7 from the participating schools. The rest of the cases were split between groups 2 and 6 to make a total of 400 with equal numbers in each of the two age groups. Children were not selected if parents had indicated a wish not to be contacted further on the appropriate portion of the questionnaire. Some children had moved school and were replaced by children in group 1 not in the original selection. Selection of children from groups 1, 2, and 6 was random. Three children, thought by the administration to still be at the school, turned out to have left when the school was visited for testing, reducing the test selection to 397.

Parents were sent an explanatory leaflet together with a consent form at least two weeks before testing was due to take place. Ethical approval was obtained from the Southampton University and Hospital's ethics subcommittee.

BRONCHIAL PROVOCATION TESTING

The methodolgy of Yan *et al* was chosen for its simplicity and ease of use in the field.[1] Methacholine was used as the provoking agent because of its lower incidence of side effects, stability in solution, and economy. On a molar basis its potency as a bronchoconstrictor agent is reputed to be similar to that of histamine.[11] The DeVilbiss No 40 hand held nebulisers were used (DeVilbiss). The mean output of the nebuliser per actuation was calculated for each unit by weighing the nebuliser before and after 100 consecutive aerosol deliveries. The procedure was carried out on five separate days to calculate the day to day repeatability in the form of a coefficient of variation. In addition, serial measurements of mean output per actuation were made by weighing before and after 10 puffs on 10 successive occasions from which could be calculated the coefficient of variation from one actuation to another. A number of nebulisers were tested and the best four chosen for delivery of the methacholine solutions in the study. The information obtained from these measurements is summarised in table 2.

Increasing doses of methacholine were administered to subjects using one to six puffs from the four nebulisers containing varying concentrations of methacholine solution. The methodology for testing has been described in detail elsewhere.[1 12] After an initial inhalation of normal saline subjects were

Table 2 *Aerosol output data on the four nebulisers used in the study*

	Nebulisers			
	1	*2*	*3*	*4*
Output/puff (ml$\times10^{-3}$)	3·13	2.30	2·07	1·98
Coefficient of variation/puff (%)	17	9	17	12
Coefficient of variation/day (%)	2	3	2	3
Required output/puff (μmol)	0·8	0·4	0·1	0·025
Solution concentration (M)	0·255	0·174	0·048	0·013
Solution concentration (g%)	5·00	3·40	0·947	0·248

given increasing doses of methacholine from 0·025 μmol to 6·4 μmol. The dose given was expressed cumulatively by including previous doses. Where a history of moderate to severe asthma was given, doubling doses were used. In the remaining subjects quadrupling doses were used initially—moving to a doubling dose regime if a fall of 10% from the postsaline value occurred. The test was continued until either the highest dose had been administered or a greater than 20% drop in forced expiratory volume in one second (FEV$_1$) from the postsaline measurement had been recorded. Any bronchoconstriction caused by the methacholine was then reversed with inhaled salbutamol via a 750 ml valved spacer device (Volumatic, Allen and Hanburys). The cumulative provocation dose of methacholine required to cause a 20% fall in FEV$_1$ from postsaline baseline (PD$_{20}$ methacholine) was calculated from a log dose response curve by linear interpolation. Children were divided into two groups according to whether they showed bronchial responsiveness to ≤6·4 μmol of methacholine, the top dose used. Eighteen children did not undergo bronchial provocation testing because they had an initial FEV$_1$ of <75% expected for height. Fourteen of these showed reversability of airways obstruction by a >10% rise in FEV$_1$ in response to salbutamol. A further child showed a fall in FEV$_1$ of >20% in response to the forced expiratory manoeuvre but reversed with salbutamol. For the purposes of analysis we included these 15 children within the group who showed bronchial responsiveness to methacholine.

The repeatability of the test was measured by testing 32 children on two separate occasions: on successive days in nearly all cases and in all cases within one week. Three children fell outside the range of the test on one or both days. Results were thus obtained on 29 children. It was also possible to retest a further 13 children using the classical method of Cockcroft *et al* to derive an estimate of comparability between the two challenge methods.[13]

SKIN TESTING

Allergen diluent and histamine controls together with three allergen extracts—house dust mite (*Dermatophagoides pteronyssinus*), mixed grass pollens, and cat dander (Bencard)—were used for intradermal testing. These allergens were chosen because they have previously been shown to identify >98% of atopic children in the United Kingdom.[14,15] The skin was pricked through the forearm using a sterile 25 gauge needle without drawing blood. Any weals produced by the control solutions or allergen extracts were measured after 10 minutes and the diameters recorded. Those with diameters ≥3 mm were scored positive. Children were excluded if the allergen diluent control produced a weal of ≥3 mm or if the histamine control failed to produce a weal greater than the diluent control. Children with one or more positive result were classed as atopic.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences edition X was used for categorisation and analysis of data.[16]

Results

RESPONSE RATES

The 397 test appointments represented one sixth of the 2503 replies to the questionnaire but, because of the selection procedure, a higher proportion of the symptomatic children (table 1). Of these 341 (86%) attended for testing with the consent of their parents. Four children refused bronchial provocation testing and seven were unable to perform the test manoeuvres. Thus 97% of children attending were successfully tested for bronchial responsiveness and comprised 83% of all children selected. Four children refused skin testing and in five further cases results were not recorded in error; results were thus obtained for 332 children (84% of selected children, 97% of attenders). Skin test results from three children were excluded because of inappropriate control results.

Methacholine did not cause a hoarse voice or flushing as occurs with high concentrations of histamine.[11] After methacholine challenge there were no cases of severe bronchoconstriction and in all children rapid reversal occurred after inhalation of salbutamol. Three children complained of dizziness thought to be related to hyperventilation. One child became briefly tearful during testing but quickly recovered and completed the test with the encouragement of her mother. The major complaint from nearly all the children reaching the top concentration of methacholine was its bitter taste. Many children required considerable encourage-

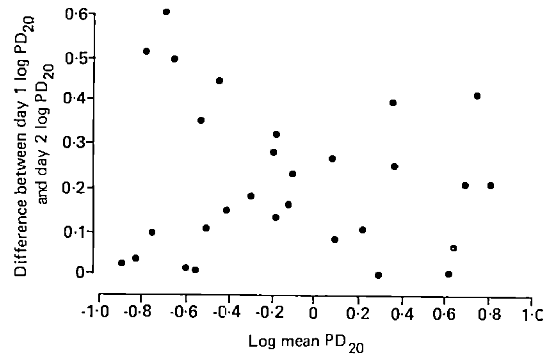

Figure *Difference between two sereial PD_{20} methacholine measurements plotted against mean PD_{20}. (Altman and Bland.[17])*

ment to complete the test because of this characteristic.

REPEATABILITY AND COMPARABILITY

The difference between the two repeat measurements of log PD_{20} is plotted against the mean log PD_{20} in the figure. It can be seen that there was no association between the size of the difference and the responsiveness of the subject, thus justifying the use of a *t* distribution to describe the repeatability of the method.[17] The standard deviation of the difference day 1 log PD_{20} − day 2 log PD_{20} was 0·256 giving a 95% confidence interval of 0·524 equivalent to 1·74 doubling concentrations or a factor of 3·34.

Two of the children retested using the Cockcroft method were excluded because of changes in asthma control between tests resulting in large changes in bronchial responsiveness so that data was available on 11 children. The Cockcroft method gives a result in terms of concentration of methacholine (nebulised over a fixed interval) producing a 20% fall in FEV_1 (PC_{20}). The mean difference log PD_{20} − log PC_{20} was 0·385 equivalent to a factor of 2·4 or 1·3 doubling concentrations. Thus multiplication of the PD_{20} value in μmol by 2·4 gives an approximate conversion factor for the PC_{20} in mg/dl using the Cockcroft method.

ATOPY AND BRONCHIAL RESPONSE TO METHACHOLINE

The proportion of children shown to have bronchial responsiveness to ≤6·4 μmol of methacholine (bronchial responsiveness to methacholine) and the proportion designated as atopic based on the results of the allergen skin tests are displayed in table 3. The estimated prevalences for the whole population have been derived from the known proportion of each symptom group within the total population (table 1) and confidence intervals calculated from the summed variances for each group.

In view of a probable relationship between symptoms and both bronchial responsiveness to methacholine and atopy,[18] the Mantel-Haenszel test[19] was used to control for symptoms when examining the association between bronchial responsiveness to methacholine and atopy. We also controlled for age group in view of alterations in the prevalences of atopy and bronchial responsiveness to methacholine with age (table 3). Bronchial responsiveness to methacholine remained highly significantly related to atopy when we controlled for these two factors ($p<0·0001$). The same test was used to measure the significance of the negative association between age and bronchial responsiveness to methacholine controlling for symptoms and atopic status. This association was also found to be highly significant ($p=0·0028$). Similarly the positive association between atopy and age was significant ($p=0·0052$) when controls were made for symptoms

Table 3 *Proportions of children displaying bronchial responsiveness to methacholine or with one positive skin allergen test*

Symptom group	*Bronchial responsiveness to methacholine*		*Atopy*	
	*Age 7 years % (No)**	*Age 11 years % (No)**	*Age 7 years % (No)**	*Age 11 years % (No)**
1 None	17·5 (40)	5·0 (40)	25·0 (40)	22·0 (41)
2 Cough alone	39·4 (33)	13·6 (22)	21·9 (32)	27·3 (22)
3 Wheeze with or without cough	43·5 (23)	64·3 (28)	52·2 (23)	68·0 (25)
4 Shortness of breath with or without cough	36·4 (11)	7·7 (13)	27·3 (11)	53·8 (13)
5 Wheeze and shortness of breath with or without cough	52·9 (17)	70·0 (40)	52·9 (17)	77·5 (40)
6 Bronchial irritability†	30·3 (33)	14·3 (21)	14·7 (34)	27·3 (22)
7 Past wheeze/shortness of breath		33·3 (9)		33·3 (9)
Estimated % prevalence in whole population (95% confidence interval)	29·1 (21·9 to 36·3)	16·5 (11·1 to 21·9)	26·0 (18·8 to 33·2)	31·6 (23·8 to 39·4)

*Percentage of number of children (No) tested in that symptom group.
†See text for explanation of symptom group.

and the presence of bronchial responsiveness to methacholine. However, there were no significant associations between sex of the child and methacholine bronchial responsiveness or the presence of atopy.

Discussion

We have confirmed the feasability of a method for bronchial provocation testing of children on a large scale in the field. While hoarse voice and flushing has been commonly reported as a problem with higher doses of histamine, methacholine is said to have no undesirable side effects.[11] In this study of schoolchildren we did encounter difficulties with the bitter taste of methacholine. This side effect was a potential source of difficulty and many children needed considerable encouragement to complete the six inhalations necessary for the last dose of methacholine. This exaggerated response was not predicted given the mildness of the taste to an adult and should, therefore, be taken into account in future studies involving children.

We have tested the repeatability of our methodology for bronchial provocation testing and have achieved results comparable with those obtained by Britton *et al* in a study of adults.[2] The fact that repeated measurement of bronchial responsiveness can only produce results within a factor of three or more of each other should guard against over interpretation. For this reason as well as simplicity, we have divided children into those with PD_{20} values of less than or greater than 6·4 µmol of methacholine, the top dose used in this study. We have thus been able to show that one group of children is more responsive to methacholine than another but not by how much. In a similar way we have classified children into atopic and non-atopic groups rather than endeavouring to produce a potentially misleading 'atopy index'. This has allowed us to test the significance of our findings using simple and reliable statistical tests designed for the analysis of categorical data.

We have used our data on the individual outputs of the nebulisers to calculate the concentrations needed for the required delivery of methacholine. Yan *et al* assumed a common output of 0·003 ml for each nebuliser, although their data showed that this was not the case.[1] In the present study all methacholine provocation tests were performed by a single operator using the same set of nebulisers. For epidemiological studies in which several operators are used, it would seem wise to measure the outputs of each set of nebulisers with the operators using them and to adjust the concentrations of provoking solution accordingly. Such an approach may improve reliability as well as comparability between studies using simlilar equipment. We recommend that a set of nebulisers is chosen with an output coefficient of variation of <20%.

Our data gives a prevalence of 29·1% at 7 years and 16·5% at 11 years for a PD_{20} for methacholine of less than 6·4 µmol. This compares well with a recent study by Salome *et al* using similar methodology where 17·8% of 8–11 year old Australian schoolchildren had a PD_{20} for histamine of less than 7·8 µmol.[20] Methacholine has been said to have a similar molar potency to histamine when used for bronchial provocation.[11] The concordance between these studies suggests that this is indeed likely to be the case. This is an important consideration because of the almost interchangeable way in which the two substances have been used in different studies.

The prevalence of atopy in this study of 26% at 7 years and 31·6% at 11 years is comparable with the prevalence of 33·7% found by Godfrey and Griffiths for positivity to house dust mite or grass pollen among 303 Southampton children aged 8 to 14 years.[21] The slightly higher prevalence of atopy to just two allergens recorded by Godfrey and Griffiths together with the higher age range suggests that the increase in prevalence recorded in our group between 7 and 11 years may continue to 14 years.

The differences in bronchial responsiveness to methacholine and atopy found between the two age groups reached a high level of significance but, surprisingly, occurred in opposite directions despite a strong association between atopy and bronchial responsiveness to methacholine. An age related change in bronchial responsiveness has not been previously reported. It is possible for apparently significant associations between unrelated variables to occur in epidemiological studies by chance where an undiscriminating examination has been made of any possible interactions between a large number of variables. In this study, however, only a small number of interactions were examined based upon hypothesis testing, in particular: those between atopy and bronchial responsiveness to methacholine and between each of these measurements and age, sex, and three respiratory symptoms. It is unlikely that the differences in bronchial responsiveness to methacholine and atopy observed between the two ages is due to other differences between the two groups as the method of selection was random with a broad spectrum between a large number of schools. The numbers of children within each symptom group were necessarily different but we have controlled for this in our analyses.

It might be thought likely that differences in bronchial responsiveness between the two ages could be the result of differences in airway calibre.

Although bronchial responsiveness has been widely studied, there is no reported interaction with height, indeed such an interaction would invalidate a number of studies now reported in the literature in adults, children and infants. Airway resistance varies with the fourth power of diameter, although the association is more complex during turbulent flow which may occur during a forced manoeuvre. However, tests of bronchial responsiveness depend upon a standard *change* in airway resistance (usually resulting in a 20% fall in FEV_1). A given percentage change in airway diameter will result in a larger percentage change in airway resistance but the association between the two will be the same for airways of different sizes providing that there are not substantial differences with respect to turbulent flow and airway closure. The latter assumption is not unjustified as the use of a 20% fall in FEV_1 as our endpoint required only a minimal degree of bronchoconstriction. It is also improbable that the difference between the two ages is dose related as the variation in size between the children would be grossly outweighed by the use of doubling doses of bronchoconstrictor agent.

The high rate of atopy and the presence of bronchial hyper-responsiveness in asthmatic children and adults is well described,[22 23] and therefore our finding of a statistical association between the two phenomena is not surprising. In this study we have further shown a highly significant association between the presence of bronchial hyper-responsiveness and atopy which, in being independent of symptoms, indicates a likely interaction between the two phenomena. However, the contrast between the rise in atopy and fall in bronchial responsiveness between 7 and 11 years supports the view that bronchial hyper-responsiveness and atopy are two independently occurring phenomena which nevertheless have important interactions with each other. These age related changes contrast with the absence of a significant change in wheeze prevalence between 7 and 11[1] perhaps indicating that they counteract each other.

We failed to show any association between gender and either bronchial responsiveness or atopy. In the questionnaire part of the study a highly significant association between gender and wheeze was shown among two and half thousand children.[10] The difference was, however, small and the power of the study high. The smaller numbers of children tested for atopy and bronchial responsiveness mitigated against showing a similar small difference.

In this study we have shown that reliable information may be obtained from bronchial provocation testing of primary school children using simple equipment in the field. Our data indicates a decrease in bronchial responsiveness between 7 and 11 years in contrast with an increase in atopy. Nevertheless atopy and bronchial responsiveness have a close statistical association even when controlling for the presence of respiratory symptoms including wheeze. Careful analysis of the inter-relationships between these variables is necessary to elucidate the nature of this interaction and its significance.

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References

[1] Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;**38**:760–5.

[2] Britton J, Mortagy A, Tattersfield A. Histamine challenge testing: a comparison of three methods. *Thorax* 1986;**41**:128–32.

[3] Mortagy AK, Howell JB, Waters WE. Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma. *Br Med J* 1986;**293**:525–9.

[4] Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;**286**:1256–8.

[5] Sears MR, Jones DT, Holdaway MD, *et al.* Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986;**41**:283–9.

[6] Cockcroft DW, Ruffin PE, Dolovich J, Hargreave FE. Allergen induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977;**7**:503–13.

[7] Cartier A, Bandouvaki J, Ryan G, Dolovich H, Hargreave FE. Asthma and increased non-allergic bronchial responsiveness to methacholine during natural exposure to ragweed pollen. *Am Rev Respir Dis (Suppl)* 1980;**121**:61.

[8] Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increase in non-allergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol* 1983;**71**:399–406.

[9] Platts-Mills TA, Tovey ER, Mitchell EB, Mozarro H. Long term effects of living in a dust free room on patients with allergic asthma—reversal of bronchial hyperreactivity. *Monogr Allergy* 1983;**18**:153–5.

[10] Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. *Arch Dis Child* 1989;**64**:1118–25.

[11] Woolcock AJ, Yan K, Salome C. Methods for assessing bronchial reactivity. *Eur J Respir Dis* 1983;(suppl 128)**64**: 181–94.

[12] Clifford RD, Pugsley A, Radford M, Holgate ST. Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children. *Arch Dis Child* 1987;**62**:66–73.

[13] Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;**7**:235–43.

[14] McCarthy OR. Selection of skin tests in asthma. *Br J Dis Chest* 1973;**67**:238–40.

[15] Russel G, Jones SP. Selection of skin tests in childhood asthma. *Br J Dis Chest* 1976;**70**:104–6.

[16] *SPSSx users guide.* 2nd ed. New York: McGraw-Hill, 1986.

[17] Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *The Statistician* 1983;**32**:307–17.

[18] Clifford RD, Howell JB, Radford M, Holgate ST. Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. *Arch Dis Child* 1989;**64**:1133–9.

[19] Snecdor GW, Cochran WG. *Statistical methods*. 6th ed. Iowa: Iowa State University Press, 1967:255–6.
[20] Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren—I. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;**17**:271–81.
[21] Godfrey RC, Griffiths M. The prevalence of immediate positive skin tests to Dermatophagoides pteronyssinus and grass pollen in schoolchildren. *Clin Allergy* 1976;**6**:79–82.
[22] Burney PGJ, Britton JR, Chinn S, *et al*. Descriptive epidemiology of bronchial reactivity in an adult population: results from a community survey. *Thorax* 1987;**42**:38–44.
[23] Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren—II. Relative importance of aetiological factors. *Clin Allergy* 1987;**17**:283–90.

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Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren

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SUMMARY Data on respiratory symptoms were obtained on 2503 schoolchildren aged 7 and 11 in Southampton by means of a self administered parental questionnaire. Children were classified into seven symptom groups from which 330 were tested for bronchial responsiveness to ≤6·4 μmol methacholine and skin tested for the presence of atopy. The symptoms of wheeze, cough, and shortness of breath were all significantly associated both with each other and bronchial responsiveness to methacholine but only wheeze was associated with atopy. The association of wheeze with both bronchial responsiveness to methacholine and atopy remained highly significant when controlling for the symptoms of cough and shortness of breath. Neither cough nor shortness of breath, however, were significantly related to bronchial responsiveness to methacholine when controlling for the symptom of wheeze. This study therefore calls into question the epidemiological relevance of these two symptoms as diagnostic features of asthma, particularly in the absence of wheeze, although they may be useful indicators of morbidity.

Wheeze was not related to bronchial responsiveness to methacholine in the absence of atopy or to atopy in the absence of bronchial responsiveness to methacholine but was strongly related to the combination of the two phenomena. The presence of these three characteristics could therefore indicate a discrete disease entity. The decrease in the prevalence of cough between 7 and 11 years appeared to be mirrored by a similar decrease in the prevalence of wheeze when the symptom was not associated with the combination of bronchial responsiveness to methacholine and atopy. On the basis of these findings and those of others we suggest that the latter group may represent children with a separate disease entity(ies) or with residual symptoms secondary to acute viral or other infections of the lower respiratory tract.

The epidemiology of asthma is of importance in the study of both temporal and geographical changes in the prevelance of the disorder and its possible causes.[1] Cross sectional studies of asthma prevalence using subject recall of previous medical diagnoses have failed to achieve their aims largely because of the frequent underdiagnosis of the condition.[2] Although studies of childhood asthma which have concentrated upon the symptom of recurrent wheeze have provided much useful information, the precise association of the prevalence of this symptom to the prevalence of asthma is unknown. Some children with asthma present with symptoms other than wheeze, although it is not known how many of these would answer negatively to a question on the symptom. On the other hand intermittent symptoms similar to asthma are known to occur for years after acute episodes of bronchiolitis[3 4] and pertussis,[5] but disappear with increasing age[3 4] and are probably unrelated to the presence of atopy[6 7] or a family history of asthma.[7]

The provocation of acute airways obstruction using non-specific agents such as exercise, inhalation of cold air, histamine, or methacholine as indirect or direct indices of non-specific bronchial responsiveness has a long history in the study of asthma but has only recently been used in large scale epidemiological studies in adults[8] and children.[9] However, the association of non-specific bronchial hyperresponsiveness to asthma is no clearer than that of wheeze. For instance, a large overlap is known to occur in levels of measurable bronchial responsiveness between asymptomatic and clearly symptomatic individuals and is particularly obvious in children.[10] There have been a number of studies linking the presence of atopy to asthma but the role of this immunological abnormality as a defining characteristic of asthma is also unclear.

We have previously described the results of a questionnaire survey of respiratory symptoms in 2503 Southampton schoolchildren[11] and in a second paper the results of methacholine bronchial provocation with allergin skin testing of 332 of the same children selected on the basis of symptom group.[12] We now present the associations found between symptoms and the results of bronchial provocation and allergen skin testing in 7 and 11 year old children from the same population.

Subjects and methods

QUESTIONNAIRE STUDY

All children within the age groups 6·8–7·8 years (7 year olds) and 10·8–11·8 years (11 year olds) in 55 schools in the urban environment of Southampton were included in the study. The questionnaire, which has been described elsewhere,[11] contained questions designed to identify current and past symptoms of wheeze, shortness of breath, and cough in addition to provoking factors.

BRONCHIAL PROVOCATION AND ALLERGIN SKIN PRICK TESTING

Children were placed into one of seven mutually exclusive symptom groups according to the answers provided on the respiratory questionnaire (table 1).[12] These groups mainly related to the symptoms of wheeze, cough, and shortness of breath but also included a group of children whose parents had answered negatively to those sections of the questionnaire but positively when asked about the effect of a number of environmental irritants. For brevity, this group was classed as having 'bronchial irritability'. With the exception of group 7, each symptom group referred to symptoms within 12 months from delivery of the questionnaire. Four hundred children were selected from these groups for methacholine bronchial provocation and allergen skin prick testing of whom 341 attended, 330 being successfully tested for bronchial responsiveness and 329 for atopy.[12]

The methodologies used for the bronchial provocation and allergen skin prick tests have been described in detail elsewhere.[12] [13] The cumulative provocation dose of methacholine required to cause a 20% fall in forced expiratory volume in one second (FEV_1) from a postsaline baseline (PD_{20} methacholine) was calculated from the log-dose response curve by linear interpolation. As most children did not respond to even high doses of methacholine, they were divided into those with PD_{20} values of less than or greater than 6·4 µmol, the top dose of constrictory agonist used in this study. It was thus possible to show that one group was more methacholine responsive than another but not by how much. For convenience we have classified these children with a PD_{20} methacholine of ≤6·4 µmol as having the characteristic of bronchial responsiveness to methacholine but the arbitrary nature of this classification should not be forgotten. Fifteen children with an FEV_1 <75% expected for height were not tested but showed reversability with salbutamol. These children were therefore classified within the group with bronchial responsiveness to methacholine for the purpose of analysis.

Table 1 *Proportion of children within each symptom group, response to methacholine, and allergen skin testing*

Symptom group	*Bronchial responsiveness to methacholine % (No)**	*Atopy % (No)**
1 None	11·3 (80)	23·5 (81)
2 Cough alone	29·1 (55) 1	24·1 (54)
3 Wheeze with or without cough	56·3 (48) 2	56·9 (51) 2
4 Shortness of breath with or without cough	20·8 (24)	41·7 (24)
5 Wheeze and shortness of breath with or without cough	64·9 (57) 2	70·2 (57) 2
6 Bronchial irritability†	24·1 (54)	19·6 (56)
7 Past wheeze/ shortness of breath	33·3 (9)	33·3 (9)

*Percentage of number of children tested (No) in that symptom group who displayed the characteristic.
†See text for explanation of symptom group.
χ^2 tests: all symptoms v atopy: p<0·001; all symptoms v bronchial responsiveness to methacholine: p<0·001; each symptom group v no symptoms: 1, p<0·02: 2, p<0·0001: other differences not significant.

Three allergen extracts, house dust mite (*Dermatophagoides pteronyssinus*), mixed grass pollens and cat dander (Bencard) were used for skin prick testing. Children with one or more positive results, when compared with appropriate controls, were classed as atopic.[14] [15]

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences edition X was used for categorisation and analysis of data.[16] Correlations between variables were calculated using χ^2 analyses and the Mantel-Haenszel test where appropriate.[17]

Results

Bronchial responsiveness to methacholine, as defined above, was shown to occur in 111 (33·6%) of the 330 children tested and a positive immediate response to allergen skin testing (atopy) was found in 125 (38·0%) of 329 children tested. The two symptom groups containing children with wheeze (table 1: groups 3 and 5) included the highest proportions with bronchial responsiveness to methacholine and with atopy. Testing by χ^2 of the overall association between symptoms and bronchial responsiveness to methacholine showed this to be highly significant ($p<0·001$). The associations between symptoms and the presence of a positive skin response to each of the three allergens was also highly significant ($p<0·001$ in each case). When compared with children without symptoms, the associations between the reported symptom of wheeze and bronchial responsiveness to methacholine and between wheeze and atopy were highly significant. Nevertheless of 105 children with wheeze, 42 did not display bronchial responsiveness to methacholine and 39 of 108 were found not to be atopic. The strength of the associations between wheeze and bronchial responsiveness to methacholine and between wheeze and atopy appeared to be greater in the presence of shortness of breath but these were not significant observations. A significant association was found between bronchial responsiveness to methacholine and the symptom group 'cough alone' ($p<0·02$) but this did not correlate with the presence of atopy. The small number of children in the shortness of breath alone group prevented adequate assessment of the significance of the symptom on this analysis.

The results of the questionnaire survey showed that wheeze, cough, and shortness of breath were all associated with each other ($p<0·001$ for each association controlling for the remaining symptom group). The data were therefore further analysed by respiratory symptom (wheeze, cough, or shortness of breath) controlling for the presence of the other two symptoms. This also allowed us to examine all children in groups 4 and 5 (table 1) with respect to shortness of breath by controlling for wheeze and cough. In this analysis wheeze remained strongly related to both bronchial responsiveness to methacholine ($p<0·0001$) and atopy ($p<0·0001$) when controlling for the symptoms of cough and shortness of breath. By contrast, when controlling for wheeze, the symptoms of cough, shortness of breath, and 'bronchial irritability' all failed to show significant associations with either bronchial responsiveness to methacholine or atopy (tables 2 and 3).

We had previously found that bronchial responsiveness and atopy were closely related even when controlling for symptoms.[12] We therefore tested the independence of the associations between wheeze and atopy and between wheeze and bronchial responsiveness to methacholine. Overall wheeze remained strongly related to atopy when controlling

Table 2 *Effect of wheeze on the proportion of children with bronchial responsiveness to methacholine controlling for the presence of other symptoms*

	*Wheeze absent % (No)**	*Wheeze present % (No)**
Shortness of breath:		
Absent	20·7 (198)	54·9 (51)
Present	20·8 (24)	64·9 (57)
Cough:		
Absent	17·3 (150)	65·4 (26)
Present	27·8 (72)	58·5 (82)
Bronchial irritability:		
Absent	16·0 (106)	87·5 (8)
Present	25·0 (116)	58·0 (100)

*Percentage of number of children tested (No) with each symptom combination who displayed bronchial responsiveness to methacholine.

Mantel-Haenszel tests: wheeze *v* bronchial responsiveness to methacholine controlling for shortness of breath, cough, and bronchial irritability: $p<0·0001$; shortness of breath, cough, and bronchial irritability *v* bronchial responsiveness to methacholine controlling for wheeze: all not significant.

Table 3 *Effect of wheeze on the proportion of children with atopy controlling for the presence of other symptoms*

	*Wheeze absent % (No)**	*Wheeze present % (No)**
Shortness of breath:		
Absent	23·0 (200)	60·4 (48)
Present	41·7 (24)	70·2 (57)
Cough:		
Absent	22·9 (153)	76·0 (25)
Present	29·6 (71)	62·5 (80)
Bronchial irritability:		
Absent	23·6 (106)	75·0 (8)
Present	26·3 (118)	64·9 (97)

*Percentages of number of children tested (No) with each symptom combination who displayed atopy.

Mantel-Haenszel tests: wheeze *v* atopy controlling for shortness of breath, cough, and bronchial irritability: $p<0·0001$; shortness of breath, cough, and bronchial irritability *v* atopy controlling for wheeze: all not significant.

for the presence of bronchial responsiveness to methacholine (p<0·0001) and to bronchial responsiveness to methacholine when controlling for atopy (p<0·0001). It was clear during this analysis, however, that wheeze was not related to atopy in the absence of bronchial responsiveness to methacholine or to bronchial responsiveness to methacholine in the absence of atopy (tables 4 and 5). Thus while 57 of 69 (82·6%) atopic children with wheeze displayed the characteristic of bronchial responsiveness to methacholine, this was only true of five of 35 (14·3%) children with wheeze but who were not atopic (table 4). Similarly 57 of 62 (91·9%) wheezers with bronchial responsiveness to methacholine were atopic compared with 12 of 42 (28·6%) of those who did not respond to methacholine. In the absence of atopy (table 5), more children with any reported respiratory symptom displayed bronchial responsiveness to methacholine compared with asymptomatic children but this difference just failed to reach significance (Fisher's exact test: p=0·074).

A comparison was made between the two age groups of children with the current symptom of wheeze with respect to the presence or absence of the combination of bronchial responsiveness to methacholine and atopy. It was found that 61·5% (24/39) of the 7 year old children with wheeze did not have both of these characteristics while this figure decreased to 35·4% (23/65) in the 11 year olds (p=0·017). Although failing to reach significance, these figures suggest that a fall in the prevalence of wheeze which is unassociated with bronchial responsiveness to methacholine and atopy may occur between 7 and 11 years mirroring the fall in the prevalence of cough.[11]

Table 4 *Effect of wheeze on the proportion of children with atopy controlling for the presence of bronchial responsiveness to methacholine*

	*Wheeze absent % (No)**	*Wheeze present % (No)**	*p Value (χ^2)*
Atopy absent	15·4 (162)	14·3 (35)	NS
Atopy present	35·7 (56)	82·6 (69)	<0·001

*Percentages of number of children tested (No) with each combination who displayed bronchial responsiveness to methacholine.

Table 5 *Effect of wheeze on the proportion of children with bronchial responsiveness to methacholine controlling for the presence of atopy*

	*Wheeze absent % (No)**	*Wheeze present % (No)**	*p Value (χ^2)*
Bronchial responsiveness to methacholine:			
Absent	20·8 (173)	28·6 (42)	NS
Present	44·4 (45)	91·9 (62)	<0·001

*Percentages of number of children tested (No) with each combination who displayed atopy.

Discussion

We have performed a questionnaire survey of respiratory symptoms including wheeze among over 2500 schoolchildren of 7 and 11 years and in nearly 330 have performed tests of bronchial response to methacholine and skin sensitivity to three common allergens with the aim of discovering the associations between these variables and suggesting their role in the epidemiological definition and study of asthma.

Two factors examined in the first paper were found to be strongly related to the prevalences of respiratory symptoms[11]: the presence of parental asthma and the sex of the responder to the questionnaire. We have not controlled for either of these factors which did not, in any case, enter into our randomised selection of children for testing. Either parental asthma or sex of responder might result in over or under reporting of symptom prevalences. In simple terms, this means that either could affect the precision with which the parent has answered the questionnaire. Clearly, this is not measurable and could be altered by any number of other factors. Imprecision may have blurred some weak associations but is not likely to have strengthened those described in this report or created associations which are not there—this would be a matter of chance which, therefore, has been measured by the statistical tests described. Although parents were told that testing would take place on some of the children, the nature of the tests was not outlined in the literature accompanying the initial questionnaire. Clearly, parents could not, in any case, have known the results of the tests to be performed on their children the following term. It is possible that the relationship between the sex of the responder to the questionnaire and the symptoms reported represents under or over reporting by fathers and mothers respectively. However, informal discussion with parents who attended with their children revealed a tendency for the mother or both parents together to complete the questionnaire if the child suffered significant symptoms.

The data presented in this and the preceding papers include a number of interesting negative findings. Mortagy *et al* were successful in finding a group of respiratory symptoms within the adult population which appeared to be universally associated with a defined degree of bronchial responsiveness (nocturnal dyspnoea, morning tightness lasting longer than one hour, and shortness of breath or wheeze in response to environmental irritants and cold). One of the aims of the present study was to find a similar group of symptoms which could be reported by parents in their children. In view of the close associations found by Mortagy *et al*,[18] it was surprising to find that none of the symptoms described by the latter group, or any symptom other than wheeze, could be shown to have any separate association with either bronchial responsiveness or atopy. Our inability to corroborate the findings of Mortagy *et al* may indicate a difference between the paediatric and adult populations. Alternatively, it may simply indicate the fundamental difference between the subjective reporting of symptoms by adults and the objective nature of parent's observations. The children within our study population, however, were within an age range who would be able to report their symptoms to their parents. It is likely that further studies in adults, which may or may not corroborate the findings of Mortagy *et al*, will be required before these questions can be answered.

The absence of an association between symptoms other than wheeze and either methacholine bronchial responsiveness or atopy mirrored our previous finding that neither cough nor shortness of breath were related to parental asthma when we controlled for the symptom of wheeze.[11] This finding was not altered by confining our analyses to symptoms occurring at night or in the morning or in response to environmental irritants. In view of the commonplace occurrence of both shortness of breath and cough in known asthmatics, this is an unexpected finding. In contrast, the associations between wheeze and parental asthma, bronchial responsive to methacholine and atopy were highly significant. Although children with asthma may present with the symptoms of cough or shortness of breath, most if not all of these will be found to have the additional symptom of wheeze on direct questioning. In the absence of wheeze, these findings indicate that the significance of cough or shortness of breath in relation to the diagnosis of asthma should be regarded with caution in future epidemiological work in children, although their usefulness as markers of morbidity is not in doubt. These data would also suggest that the treatment of children, who complain of recurrent cough, for asthma when there are no other indicators of the disease should be regarded with circumspection particularly in view of the commonness of this symptom.[11]

This study has shown an intriguing inter-relationship between the symptom of wheeze and the characteristics of bronchial responsiveness to methacholine and atopy. We have previously shown that bronchial responsiveness to methacholine and atopy remained strongly associated when controlling for wheeze, suggesting either a causal interaction or a common defect. The associations between wheeze and both bronchial responsiveness and atopy are well known. However, in this report we have shown that wheeze was quite unrelated to bronchial responsiveness to methacholine in the absence of atopy, despite a highly significant association among atopic children. Similarly wheeze was only related to atopy in the presence of bronchial responsiveness to methacholine but not otherwise. It would thus appear that the joint presence of these two phenomena is necessary for the manifestation of the symptom of wheeze and may represent a distinct pathological entity which is likely to be closely related to the clinical diagnosis of asthma. It is, of course, unlikely that a PD_{20} of 6·4 µmol represents a precise point below which wheeze and atopy are related; however, most responsive children had a PD_{20} between 1·6 and 6·4 µmol suggesting that a cut off point broadly exists within this range. Children below this range might be described as 'hyper-responsive' because of the close association with atopy and recurrent wheeze indicating a pathological state. A fixed cut off only represents a statistical risk factor, however, and the occurrence and severity of wheeze, even in the presence of high degrees of bronchial responsiveness and atopy, is likely to depend upon a number of additional factors.

Overall, just over half of the children with wheeze whom we tested did not display both bronchial responsiveness to methacholine and atopy. Furthermore, many children suffered with respiratory symptoms other than wheeze particularly cough. It is likely that these children occupy more than one pathological entity. It was noted in the first study that, whereas there was a sharp decline in the prevalence of cough between 7 and 11 years, the prevalence of wheeze remained unchanged. Data presented in this paper suggest that there is likely to be a parallel decline in the prevalence of wheeze when it is not associated with the combination of atopy and bronchial responsiveness to methacholine. It is now well known that children suffering a variety of respiratory insults in early life, particularly respiratory syncytial virus bronchiolitis, may have persisting respiratory problems into early school age which have usually almost resolved by the age of 10 years.[4] More recent studies have shown that these children are not more atopic than the normal population and do not have a stronger family history of asthma.[6 7] It is likely that the group of children in this study who suffered cough and wheeze unassociated with bronchial responsiveness to methacholine or atopy includes such children with symptoms subsequent to viral or other infections in infancy, and the decline in prevalence of these symptoms represents the gradual resolution reported in other studies.

We also showed a likely but again just not significant association between respiratory symptoms generally and bronchial responsiveness to methacholine in the absence of atopy. It is possible that the latter children are suffering intermittent bronchial responsiveness to methacholine—for instance, in association with viral upper respiratory tract infections. This would be more difficult to show on a single measurement and the symptoms less easy to distinguish. Certainly this study showed a high background level of bronchial responsiveness to methacholine with no associated atopy or wheeze which is otherwise difficult to explain. Many young children who later develop classical asthma symptoms wheeze only after upper respiratory tract infections with apparent complete normality between attacks. In the past this condition has been labelled 'wheezy bronchitis' but more recently has been shown to be indistinguishable from asthma in terms of allergy, family history, and prognosis.[19] It is possible that tests for atopy and perhaps serial measurements of bronchial responsiveness could be used to distinguish these children from those with symptoms subsequent to bronchiolitis and thus provide information on prognosis and perhaps treatment of the various forms of intermittent inflammatory airway disease. By performing a cross sectional survey, we have examined all our subjects over a short period of time. We have thus avoided possible differences between the two age groups which could occur as a result of year to year environmental alterations such as weather changes and fluctuations in the prevalences of viral and other respiratory infections. However, this study cannot provide information on changes occurring within individual children. A longitudinal study would be necessary to further test these hypotheses and firmly establish the natural history of the symptom subgroups in relation to atopy and bronchial hyperresponsiveness.

In the two previous papers we have shown a strong association between wheeze and the symptoms of cough and shortness of breath confirming their importance in the symptomatology of asthma. The lack of a separate association between cough, shortness of breath, or bronchial irritability as defined by Mortagy *et al*,[18] and any of bronchial responsiveness, atopy, or parental asthma when controlling for wheeze, indicates that these symptoms are not useful as epidemiological markers of the disease in childhood. We have shown a number of significant changes between the ages of 7 and 11 years, including a fall in the prevalence of cough, an increase in the prevalence of atopy, and a fall in bronchial responsiveness to methacholine, with no associated changes in the prevalence of wheeze. We have been able to separate out from this confusing picture a distinct entity characterised by wheeze in association with both atopy and a bronchial response to low doses of methacholine. Whether this syndrome represents a distinct entity or deserves the label 'asthma' is a matter of conjecture at present and clearly warrants further study.

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References

[1] Gregg I. Epidemiological aspects. In: Clark T, Godfrey S, eds. *Asthma*. 2nd ed. London: Chapman and Hall, 1983:242–78.

[2] Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *Br Med J* 1983;**286**:1253–6.

[3] Simms DG, Downham MAPS, Gardner PS, Webb JKG, Weightman D. Study of 8 year old children with a history of respiratory syncitial virus bronchiolitis in infancy. *Br Med J* 1978;**i**:11–4.

[4] Pullen CR, Hey EN. Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncitial virus in infancy. *Br Med J* 1982;**284**:1665–9.

[5] Johnston IDA, Bland JM, Ingram D, Anderson HR, Warner JO, Lambert HP. Effect of whooping cough in infancy on subsequent lung function and bronchial reactivity. *Am Rev Respir Dis* 1986;**134**:270–5.

[6] Sims DG, Gardner PS, Weightman D, Turner MW, Soothill JF. Atopy does not predispose to RSV bronchiolitis or post bronchiolitic wheezing. *Br Med J* 1981;**282**:2086–8.

[7] Webb MSC, Henry RL, Milner AD, Stokes GM, Swarbrick AS. Continuing respiratory problems three and a half years after acute viral bronchiolitis. *Arch Dis Child* 1985;**60**:1064–7.

[8] Woolcock AJ, Dowse GK, Temple K, Stanley H, Alpers MP, Turner KJ. The prevalence of asthma in the South-Fore people of Papua New Guinea. A method for field studies of bronchial reactivity. *Eur J Respir Dis* 1983;**64**:571–81.

[9] Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren—I. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;**17**:271–81.

[10] Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;**286**:1256–8.

[11] Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. *Arch Dis Child* 1989;**64**:1118–25.

[12] Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren. *Arch Dis Child* 1989;**64**:1126–32.

[13] Yan K, Salome C, Woolcock AJ. Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children. *Arch Dis Child* 1987;**62**:66–73.

[14] McCarthy OR. Selection of skin tests in asthma. *Br J Dis Chest* 1973;**67**:238–40.

[15] Russel G, Jones SP. Selection of skin tests in childhood asthma. *Br J Dis Chest* 1976;**70**:104–6.
[16] *SPSSx users guide.* 2nd ed. New York: McGraw-Hill, 1986.
[17] Snecdor GW, Cochran WG. *Statistical methods.* 6th ed. Iowa: Iowa State University Press, 1967:255–6.
[18] Mortagy AK, Howell JB, Waters WE. Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma. *Br Med J* 1986;**293**:525–9.
[19] Williams H, McNicol KN. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J* 1969;**iv**:321–5.

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Vertical transmission of HIV: a prospective study

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SUMMARY Forty nine infants of HIV seropositive women were followed up for a median of 24 months, together with 24 controls. The infection status of 11 index children under 18 months of age was indeterminate; 34 were presumed uninfected while four showed clinical and laboratory evidence of HIV disease. Based on current definitions of HIV infection and excluding children under 18 months old as well as those who had not been studied from birth, two out of 28 children were infected. The estimated rate of maternofetal transmission was therefore 7·1%. In children with proved infection, sequential laboratory data showed that hypergammaglobulinaemia was noted as early as 6 months and often predated clinical signs. This observation, in the presence of non-specific clinical findings, was helpful in alerting the paediatrician to a diagnosis of HIV infection.

Vertical transmission of the human immunodeficiency virus (HIV) is now well documented,[1–3] although the exact risk has not yet been quantified. Rates of transmission appear to vary from 22–65%, depending on inclusion criteria and duration of the study as well as methods used to define paediatric HIV infection.[4–6] The diagnostic value of an HIV antibody test is limited by the presence of passively acquired maternal antibody in infants. Clinical evidence of infection is also unreliable, especially in the early stages when signs and symptoms are non-specific.[7] The inclusion of control children is therefore essential, in order that clinical and laboratory parameters can be evaluated. So far, no study of mother to child transmission of HIV has included a control group.

In the United Kingdom, Edinburgh has been reported to have the largest population of intravenous drug users infected with HIV, one third of whom are young women.[8] Most were infected during an epidemic of needle sharing in 1983–4, and most are asymptomatic at present. Centres which reported high rates of vertical transmission of HIV had initially concentrated on women who had more advanced disease. We postulated that the same risk might not apply when the mother had preclinical disease. Infants born to HIV seropositive women were therefore enrolled into a prospective study to evaluate the risk of maternofetal transmission and to define the natural history of perinatally acquired HIV disease in those who were infected.

Subjects and methods

SUBJECT SELECTION

The paediatric counselling and screening clinic at the City Hospital in Edinburgh was established in January 1986 to monitor all infants born to HIV seropositive women. Edinburgh is one of the centres collaborating in the European Multicentre Study on perinatal transmission of HIV.

Most HIV infected pregnant women were identified in the antenatal period. If the woman chose to continue with her pregnancy, permission was sought for inclusion of her infant in the study. Thirty nine infants were thus enrolled, together with 10 who were referred either subsequent to the mother's HIV antibody test being positive, or because of symptoms suggesting HIV disease. These 49 infants comprised the index group.

Twenty four infants born to HIV seropositive fathers but whose mothers remained seronegative were included as controls. Mothers were tested after self identification of high risk activities, and belonged to similar socioeconomic groups as mothers who tested positive.

PROCEDURE AT FOLLOW UP

The procedure at follow up was identical for children in both index and control groups. Those infants identified antenatally were seen and examined at birth, at age 6 weeks, and 3 months, and at intervals of three months until the age of 2. Thereafter review occurred every six months if the child remained well. Others were seen according to the protocol from the time of referral.

At each visit, a history was taken according to a standard questionnaire and the child examined for symptoms and signs of HIV disease. Developmental screening was performed using the Denver developmental screening test. Length, weight, and head circumference were documented. Blood was then taken for laboratory tests.

LABORATORY METHODS

At intervals of three months HIV antibody was measured in both index and control children using an antiglobulin enzyme immunoassay (Abbott Recombinant HIV 1 ETA) followed by a competitive enzyme immunoassay (Wellcozyme). For index children, HIV 1 antigen was measured by quantified enzyme immunoassay (Abbott HTLV 3 antigen EIA). Lymphocytes were cultured for HIV every six months in all index children; positive results were confirmed by antigen capture.

Other investigations on peripheral blood included measurement of haemoglobin, total white cell and differential count, T lymphocyte subsets, platelet count, and immunoglobulin concentrations as previously described.[4 5]

The significance of various comparisons were tested using the χ^2 test, or Student's *t* test as appropriate.

Results

MATERNAL DATA

Characteristics of mothers of index and control children are shown in table 1. All were white. Thirty seven index mothers were infected through intravenous drug use and six were heterosexual contacts. No differences were seen between the two groups of women in the use of drugs during pregnancy, although more index mothers resorted to drug use after the birth of the child. No woman had AIDS or AIDS related illnesses before the delivery of the child, although one developed *Pneumocystis carinii* pneumonia during a third pregnancy that was terminated at 18 weeks' gestation. The remaining 42 index mothers were clinically free of HIV related symptoms. There were two sets of twins and four sibling pairs among the index children.

Table 1 *Characteristics of 43 index and 24 control mothers*

	Index *No (%)*	*Control* *No (%)*
Mean age at delivery (years)	24·1	23·6
Single mother	15 (31)	5 (21)
First born child	21 (43)	11 (45)
Drug use during pregnancy	14 (29)	2 (8)
Drug use since pregnancy	20 (41)	2 (8)*
Infant in alternative care	12 (24)	1 (4)

*$p<0.05$ (χ^2 test).

INFECTION STATUS OF INDEX CHILDREN

Four index children showed clinical evidence of HIV disease (table 2), two of whom were referred because of symptoms. All had positive cultures for HIV, with HIV antigenaemia and persistence of HIV antibody beyond 18 months of age. These children were definitely infected.

Of the remaining cohort, 11 were under 18 months of age and because of presence of maternal antibody, were classified as indeterminate status.[7] None had positive results for HIV antigen or culture. Of 38 index children over the age of 18 months, 34 were HIV antibody negative, HIV antigen as well as culture negative. They were clinically free of symptoms that suggest HIV disease and have normal tests of immune function. These 34 children were presumed uninfected.

PERINATAL DATA

Table 3 summarises perinatal data of index and control children, with the index cohort separated into children who were infected and those presumed uninfected. The mean birth weight was significantly lower in index children presumed uninfected (95% confidence interval (CI) 2714 to 3078 g) when compared with controls, (95% CI 3069 to 3527 g) and the difference remained when all children whose mothers used drugs during pregnancy were excluded from analysis. The effect of preterm delivery was allowed for by extrapolating preterm birth weight to term, along the same centile, and index children presumed uninfected were significantly lighter than controls.

All but one index infant were delivered by spontaneous vaginal delivery. Neonatal special care was required mainly for drug withdrawal symptoms and intrauterine growth retardation. Intensive care was only necessary for two index infants because of problems arising from preterm delivery. These consisted of meningitis with septicaemia resulting in ventriculoperitoneal shunts for hydrocephalus

Table 2 *Clinical and laboratory evidence of HIV infection in four children*

Sex	*Birth weight (g)*	*Gestation (weeks)*	*Symptoms/signs (age in months when first appeared)*	*Lowest absolute T4 count* ($\times 10^9$/l)	*Lowest platelet count* ($\times 10^9$/l)	*Highest IgG (g/l)*	*Outcome (age at last review)*
F	3273	42	Lymphadenopathy (6) Respiratory infections (6) Hepatomegaly (6) Failure to thrive (6) Interstitial pneumonia (9) Diarrhoea (9) Eczema (12)	0·16	79	16·0	On intravenous IgG and zidovudine (34 months)
M	930	29	Recurrent cough (8) Purpura (9) Lymphadenopathy (14) Hepatosplenomegaly (14) Night sweats (30) Parotitis (44)	0·55	14	24·0	On intravenous IgG (50 months)
F	3320	38	Respiratory infections (6) Diarrhoea (6) Lymphadenopathy (10) Recurrent fever (10) Hepatosplenomegaly (10) Pneumonia (12) Purpura (34) Dry skin (36) Molluscum (42)	0·05	50	20·8	On intravenous IgG and zidovudine (46 months)
F	2180	37	Respiratory infections (3) Diarrhoea (3) Lymphadenopathy (6) Eczema (15) Hepatosplenomegaly (15)	1·0	19	23·2	On intravenous IgG (25 months)

Table 3 *Perinatal data of 38 index and 24 control children*

	Index		*Control (n=24)*
	Infected (n=4)	*Presumed uninfected (n=34)*	
Boys	1	18	15
No with delivery <37 weeks' gestation	1	6	2
No with birth weight<10th centile	1	9	2
No who had neonatal special care	3	7	3
Mean birth weight (g)	2426	2896*	3298*
Mean birth weight (g) (excluding children whose mothers used drugs during pregnancy)	3296	3027*	3378*

*p<0·02 (Student's unpaired *t* test). Other comparisons, between index and control as well as within index children, did not reach significance.

and necrotising enterocolitis necessitating laparotomy. Cystic fibrosis was diagnosed in one index infant while another had multiple intracardiac tumours. No infant received a blood transfusion in the neonatal period, and there were no neonatal deaths. The features of HIV embryopathy were not observed in any infant.[9] Although hepatosplenomegaly was documented during the neonatal period in two index infants, this did not persist beyond three months. Two index infants were breast fed (for five and 36 weeks each) but none from the control group.

CLINICAL OUTCOME

The median age when last seen was 24 months for index infants (range 3 to 52 months), 12 months for controls (range 3 to 30 months). No child has been lost to follow up. Within the index group, children whose infection status was indeterminate have been excluded from analysis. Signs and symptoms observed in index and control children are shown in table 4, with index children separated into those infected and presumed uninfected.

Appreciable lymphadenopathy was defined as the presence of nodes >0·5 cm in diameter in more than two non-contiguous sites (excluding inguinal) and persisting beyond three months. Chronic or recurrent respiratory infections were those which occurred on three or more occasions within a three month period. Recurrent diarrhoea was defined as loose stools that persisted beyond 48 hours, required treatment, and occurred on more than one occasion per month.

Failure to thrive was diagnosed when the child's sequential weights declined across centile lines.

As seen in table 4, signs and symptoms were non-specific and were seen in control as well as index children. Lymphadenopathy and recurrent respiratory infections were seen in appreciably more index children, even those presumed uninfected, when compared with controls. All index children presumed uninfected had symptoms and signs which resolved with time; they never had positive HIV antigen or culture results.

Neurological signs were detected only in the child with neonatal meningitis (ataxic diplegia). The developmental progress of the remaining cohort was within normal limits.

LABORATORY RESULTS

Laboratory abnormalities are shown in table 5. No significant differences were seen when the index children were compared with controls. Within the index children, however, those presumed uninfected were significantly less likely to have persistent hypergammaglobulinaemia, lymphopenia, T4 lymphopenia, and thrombocytopenia. Abnormal laboratory results in index children presumed uninfected tended to be transient findings which returned to the normal range on repeat testing.

Sequential laboratory data within the index group are displayed in table 6. Hypergammaglobulinaemia was noted as early as 6 months, and often predated

Table 4 *Clinical signs and symptoms in 38 index and 24 control children*

	Index		*Control (n=24)*
	Infected (n=4)	*Presumed uninfected (n=34)*	
Significant lymphadenopathy	4*	9*	0*
Recurrent respiratory infections	4	13*	2*
Recurrent diarrhoea	4*	11*	5
Eczematous rash	3	7	1
Hepatosplenomegaly	4*	4*	0
Failure to thrive	1	3	0

*$p<0·05$ (χ^2 test). Other comparisons between index and control children, as well as within index children, did not reach significance.

Table 5 *Laboratory abnormalities in 38 index and 24 control infants*

	Index		*Control (n=24)*
	Infected (n=4)	*Presumed uninfected (n=34)*	
Hypogammaglobulinaemia	0	13	4
Hypergammaglobulinaemia	4*	4*	4
Neutropenia ($<1·0\times10^9$/l)	1	2	3
Lymphopenia ($<2·8\times10^9$/l)	3*	4*	2
T4 lymphopenia ($<1·0\times10^9$/l)	3*	0*	1
T4/T8<1·0	4*	5*	1
Thrombocytopenia ($<100\times10^9$/l)	4*	4*	0

*$p<0·05$ (χ^2 test).

Table 6 *Sequential laboratory results on index children over 18 months old*

	3 Months		*6 Months*		*9–12 Months*		*15–18 Months*		*21–24 Months*	
	Infected (n=2)	*Presumed uninfected (n=33)*	*Infected (n=2)*	*Presumed uninfected (n=25)*	*Infected (n=2)*	*Presumed uninfected (n=32)*	*Infected (n=3)*	*Presumed uninfected (n=29)*	*Infected (n=3)*	*Presumed uninfected (n=24)*
IgG (g/l)	5·20	3·66	10·30	4·08	12·70	5·59	14·63	7·08*	13·7	7·78
IgA (g/l)	0·65	0·34	1·40	0·47	1·50	0·78	1·48	0·80	1·17	0·79
IgM (g/l)	1·10	0·75	1·28	0·81	1·12	1·05	1·13	1·11	1·32	1·16
Lymphocytes ($\times 10^9$/l)	8·20	8·10	8·82	7·90	10·08	6·57	4·81	6·78	6·05	5·21
T4 lymphocytes ($\times 10^9$/l)	ND		ND		ND		0·82	2·54*	1·59	2·18
Platelets ($\times 10^9$/l)	397	376	262	362	294	305	145	336*	52	367*

The data represent mean values at each follow up interval. ND=Not done.
*$p<0·05$ Student's unpaired t test.

clinical signs. Significance was not reached until 15–18 months of age. With progression of clinical disease, other useful laboratory markers were T4 lymphopenia and thrombocytopenia.

LOSS OF MATERNAL HIV ANTIBODY

No child in the control group was HIV antibody positive at any time.

Of index infants, maternal HIV antibody was lost from 6–18 months, median 12. Thirty four children over 18 months of age remained antibody negative. They were also HIV antigen as well as culture negative. The follow up of these children from the time of seroreversion ranged from 3 to 33 months (median 18). Subsequent seroconversion after seroreversion has not been observed in the cohort.

RATE OF MATERNOFETAL TRANSMISSION

To calculate a transmission rate of HIV from mother to child, those children aged less than 18 months (n=11) as well as those not monitored from birth (n=10) have been excluded. Of the 28 remaining children, two showed clinical and laboratory vidence of HIV disease while 26 were presumed not to be infected. The estimated vertical transmission rate was therefore 7·1%. (95% CI 0 to 16·6%).

Discussion

Initial reports of paediatric AIDS concentrated on children who presented with end stage disease,[10–12] and they are not typical of the entire clinical range of HIV infected children. Increasing awareness and experience of children at risk of AIDS have allowed an improved classification of signs and symptoms observed in paediatric HIV infection.[7] The children in our study with proved HIV infection had common, non-specific clinical findings which might have been managed differently had they presented in another setting. The laboratory abnormalities that we observed were not exclusive to the infected children, and this again underlines the importance of regular follow up with sequential data and the inclusion of control children.

Most index mothers were infected through needle sharing during intravenous drug use. As most of these women come from areas of multiple deprivation, this is likely to adversely affect their infant's health and development. A previous study from Edinburgh of women who identified themselves as being at risk of HIV infection showed no significant differences in social characteristics of those who subsequently tested HIV positive, compared with HIV negative women.[13] Rather, similarities were seen in infant morbidity (low birth weight, intrauterine growth retardation, preterm delivery) in both groups of women, which were increased three fold when compared with the general population. Our choice of control infants was such that both groups were comparable in social and epidemiological factors, as well as maternal intravenous drug use during pregnancy. Despite that, the mean birth weight of the index infants presumed uninfected was significantly lower than that of controls, allowing for maternal drug use and prematurity. This could be a direct effect of HIV during pregnancy.

In estimating the vertical transmission rate, we had excluded children under 18 months of age, although the current recommendation is that children aged over 15 months who test antibody positive are defined as infected.[7] Our experience is that maternal antibody can persist until 18 months of age, and had we defined three such children as infected, we would have overestimated the prevalence of infection. Children referred because of HIV related symptoms would also add to an overestimate of infection. Therefore in the calculation of infection risk, only children monitored prospectively from birth were included. The risk of vertical transmission, as estimated from our data, was 7·1%, lower than that previously reported.[4-6] This could be explained, in part, by the fact that all the infected women were free of HIV related symptoms during pregnancy. Testing for HIV antigen was performed in eight mothers during pregnancy, and in 22 after delivery of the infant—all were found to be negative. Our results must be interpreted with caution, as the numbers are small and as yet, the prognosis for children aged over 18 months who lose maternal antibody is unknown. Although not observed in our cohort, children have been reported to lose antibody only to seroconvert later on in childhood,[14] while others have been documented to remain antibody negative with positive antigen tests and virus culture.[4 5 15]

Recent developments in diagnostic techniques, such as in vitro production of HIV specific antibody,[16] or polymerase chain reactions for amplification of viral DNA,[17] are still under evaluation and not routinely available. A recent study found that six of 14 asymptomatic newborns, and five of 10 seronegative children of infected mothers were positive for HIV-DNA, using the polymerase chain reaction technique.[18] Using more sophisticated tests, the numbers of infected children in our cohort could be higher. There is, however, an urgent need for improved methods to evaluate the seronegative index children who remain clinically well with normal immune function, as four mothers have embarked on subsequent pregnancies based purely on the observation that the index child was symptom free and antibody negative (presumed uninfected).

We were unable to detect any laboratory predictor of HIV disease when sequential index and control data were compared. In the children with proved infection, immunoglobulin concentrations (especially IgG) did, however, start to rise before clinical signs were obvious. Clinical manifestations are non-specific, but when seen in conjunction with laboratory abnormalities (hypergammaglobulinaemia, T4 lymphopenia, thrombocytopenia), a diagnosis of HIV infection can be strongly suspected in a child especially when mother has engaged in high risk activities.

In future, we hope to use the polymerase chain reaction to detect HIV-DNA in the index children presumed uninfected. It must be stressed that the demonstration of viral DNA sequences does not imply overt infection, as little is known about the immune response to HIV in children infected antenatally. Our study stresses the importance of continued careful follow up of all children at risk of HIV infection, to detect early markers of infection as well as to determine the outcome of those who appear symptom free.

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References

[1] Sprecher S, Soumenkoff G, Puissant F, Degueldre M. Vertical transmission of HIV in 15 week fetus. *Lancet* 1986;**ii**:288–9.
[2] Lapointe N, Michaud J, Pekovic D, Chausseau JP, Dupuy JM. Transplacental transmission of HTLV III virus. *N Engl J Med* 1985;**312**:1325–6.
[3] Jovaisas E, Koch MA, Schafer A, Stauber M, Lowenthal D. LAV/HTLV III in 20 week fetus. *Lancet* 1985;**ii**:1129.
[4] Mok JQ, Giaquinto C, de Rossi A, Grosch-Worner I, Ades AE, Peckham CS. Infants born to mothers seropositive for human immunodeficiency virus. *Lancet* 1987;**i**:1164–8.
[5] The European Collaborative Study. Mother-to-child transmission of HIV infection. *Lancet* 1988;**ii**:1039–42.
[6] Minkoff H, Nanda D, Meneg R, Fikrig S. Pregnancies resulting in infants with acquired immunodeficiency syndrome or AIDS related complex: follow-up of mothers, children and subsequent siblings. *Obstet Gynecol* 1987;**69**:288–91.
[7] Centers for Disease Control. Classification system for human immunodeficiency infection in children under 13 years of age. *MMWR* 1987;**36**:225–35.
[8] Brettle RP, Bisset K, Burns S, *et al.* Human immunodeficiency virus and drug misuse; the Edinburgh experience. *Br Med J* 1987;**295**:421–4.
[9] Marion RW, Wiznia AA, Hutcheon RG, Rubenstein A. Human T-cell lymphotropic virus type III (HTLV III) embryopathy. *Am J Dis Child* 1986;**140**:638–40.
[10] Oleske J, Minnefor A, Cooper R, *et al.* Immune deficiency syndrome in children. *JAMA* 1983;**249**:2345–9.
[11] Rubenstein A, Sicklick M, Gupta A, *et al.* Acquired immunodeficiency with reversed T4/T8 ratios in infants born to promiscuous and drug addicted mothers. *JAMA* 1983;**249**:2350–6.
[12] Scott GB, Buck BE, Leterman JG. Acquired immunodeficiency syndrome in infants. *N Engl J Med* 1984;**310**:76–81.
[13] Johnstone FD, MacCallum L, Brettle RP, Inglis JM, Peutherer JF. Does infection with HIV affect the outcome of pregnancy? *Br Med J* 1988;**296**:467.
[14] Aiuti F, Luzi G, Mezzaroma I, Scano G, Papetti C. Delayed appearance of HIV infection in children. *Lancet* 1987;**ii**:858.
[15] Borkowsky W, Krasinski K, Paul D, Moore T, Bebenroth D, Chandwani S. Human immunodeficiency virus infection in infants negative for anti-HIV by enzyme linked immunoassay. *Lancet* 1987;**i**:1168–71.
[16] Amadori A, deRossi A, Giaquinto C, Faulkner-Valle G, Zacchello F, Chieco-Bianchi L. In vitro production of HIV-specific antibody in children at risk of AIDS. *Lancet* 1988;**i**:852–4.
[17] Ou CY, Kwok S, Mitchell SW, *et al.* DNA amplication for direct detection of HTV-1 in DNA of peripheral blood mononuclear cells. *Science* 1988;**239**:295–7.
[18] Laure F, Rouzioux C, Veber F, *et al.* Detection of HIV-1 DNA in infants and children by means of the polymerase chain reaction. *Lancet* 1988;**ii**:538–41.

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Intravenous immunoglobulin in HIV infection: evidence for the efficacy of treatment

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SUMMARY Eight children with symptoms of HIV infection were treated for 12–26 months (median 14 months) with infusions of intravenous immunoglobulin (200 mg/kg) every three weeks. Significant improvement was noted in all children in terms of weight gain, number of infectious episodes, and days spent in hospital. This resulted in a 49% saving in cost on treatment compared with costs accrued previously during inpatient admissions. Immunoglobulin concentrations, which were raised at the start of treatment were not altered, and T4 counts continued to decline slowly. HIV core antigen was detected in four children before treatment, but all became core antigen negative after treatment was commenced, this effect being sustained in three. Intravenous immunoglobulin therefore has major clinical benefit, and by reducing viral activity may delay disease progression.

HIV infection in infants and children is associated with high morbidity and mortality,[1] and present therapeutic options are limited to treatment for specific infections,[2] and to zidovudine, which has many documented side effects and unknown long term sequelae.[3] As in adults, these infants may present with opportunistic infections and features suggestive of deficiencies of cellular immunity, with reversed T4/T8 ratios.[4 5] In addition, however, children commonly present with recurrent bacterial infections,[1 6] and defective humoral immunity has been shown.[7] Although serum concentrations of IgG, IgA, and IgM are typically raised,[8] panhypogammaglobulinaemia has been described.[9–11] Even in the presence of hypergammaglobulinaemia, which is attributed to polyclonal B cell activation,[12] patients behave as though they were hypogammaglobulinaemic. Hence passive immunisation in the form of intravenous immunoglobulin has been reported to be of benefit.[13 14] The aim of this study, therefore, was to make a fuller evaluation of the clinical effect of at least 12 months' treatment, to document any changes in laboratory indices of viral activity, and to assess the financial implications of committing children to maintenance treatment with intravenous immunoglobulin.

Patients and methods

Eight patients with clinical and laboratory evidence of HIV infection were identified, five of whom have been described in a preliminary report.[15] Clinical features at the start of intravenous immunoglobulin treatment are summarised in table 1. Children were treated with intravenous immunoglobulin on the basis of a history of two or more episodes of bacterial pneumonia, a three month history of recurrent or chronic upper respiratory tract sepsis or diarrhoea, or both, or symptomatic thrombocytopenia, with laboratory confirmation of HIV infection. All were treated every three weeks with 200 mg/kg of intravenous immunoglobulin supplied by Scottish National Blood Transfusion Service on a hospital day patient basis.[16]

The procedure and laboratory methods adopted at each visit were as previously described.[17]

The financial implications were calculated on the basis that the cost of intravenous immunoglobulin for a 15 kg child is £45 and materials, medical, nursing, and administrative staff time is £40; this gives a total of £85 per visit, or £1600 per year. The cost of inpatient paediatric care in south east Scotland is £960 per week.[18]

Table 1 *Clinical data*

Patient No	*Mode of transmission*	*Age at start (months)*	*Time on intravenous immunoglobulin (months)*	*Stage**	*Clinical features*
1	Vertical	9	26	P2A	Recurrent upper respiratory sepsis, diarrhoea, eczema, failure to thrive
2	Vertical	24	23	P2A	Recurrent upper respiratory sepsis, recurrent pneumonia, diarrhoea
3	Vertical	27	17	P2B	Prolonged pertussis, encephalopathy, recurrent pneumonia, diarrhoea
4	Vertical	48	17	P2D3	Recurrent pneumonia, diarrhoea, oesophageal candida, failure to thrive
5	Blood transfusion	42	16	P2C	Purpura, pneumonia, oral candida, lymphocytic interstitial pneumonitis
6	Vertical	26	14	P2C	Upper respiratory sepsis, recurrent pneumonia, lymphocytic interstitial pneumonitis, eczema
7	Vertical	36	14	P2F	Purpura, night sweats, upper respiratory sepsis, pneumonia, eczema
8	Vertical	12	12	P2F	Purpura, recurrent fever, upper respiratory tract sepsis, eczema

*Stage according to the Centers for Disease Control criteria.[25]

Results

After 12 months on treatment subjective improvement in general well being was reported in all eight patients. Case 3 showed an initial dramatic improvement in his encephalopathy, as previously described,[19] but later deteriorated to become severely handicapped before finally succumbing to a pneumonic illness 17 months into treatment. The other seven children remain well enough to attend normal school (n=2) or nursery (n=5) regularly. Table 2 summaries clinical findings before and after treatment. The number of infections sufficiently severe to require hospital review was significantly reduced on treatment, as was recurrent diarrhoea. Improvement in weight gain was seen in the cohort as a whole ($p<0\cdot01$); the most dramatic change was seen in those children in whom failure to thrive had been a presenting feature.

The total number of days spent in hospital for all eight children in the 12 months before treatment (except for case 1 in whom only nine months from birth had elapsed) was 220 (range 0–60), compared with 56 (range 0–20) in the first 12 months on intravenous immunoglobulin ($p<0\cdot001$). Assuming an unchanged rate of infection, the difference between actual and expected number of days of hospitalisation would be 181·6; this would result in a saving on inpatient costs of £24 905 compared with treatment costs of £12 800. Thus the net saving in costs of £1513/patient/year, or 49%, even without taking into consideration the travelling costs and time lost to the family in attending hospital.

Symptomatic thrombocytopenia, seen in three patients before treatment showed no immediate improvement on this dose of intravenous immunoglobulin, and a further child developed purpura while on treatment. Hypergammaglobulinaemia,

Table 2 *Clinical outcome after treatment*

	Before (median)	*After (median)*	*p Value*
Range of weight velocity (g/month)	−212 to +312 (117)	150 to 582 (300)	<0·01*
Total No of serious infectious episodes	34 (3)	6 (1)	<0·05*
Total No of episodes of pneumonia	13 (2)	4 (0)	NS
Total months of recurrent or chronic diarrhoea	49 (9)	21 (3)	<0·05*
No of patients with:			
Upper respiratory tract sepsis	8	8	NS
Eczema	5	5	NS
Significant lymphadenopathy	8	6	NS
Hepatosplenomegaly	7	8	NS
Thrombocytopenic purpura	3	2	NS

*Comparison of symptoms and signs experienced by the cohort in the 12 months before and in the subsequent 12 months after treatment.

seen in all patients before treatment, was not appreciably changed by treatment, and T4 counts continued to decline (mean (SD) T4 count at the start of treatment was 1·75 (0·5)×10^9/l, falling to 1·10 (0·31)×10^9/l at 1 year, and 0·65 (0·45)×10^9/l at 18 months).

All patients were HIV seropositive by enzyme linked immunoadsorbent assay (ELISA) and virus was isolated in culture from all eight. Four children (cases 1, 2, 4, 8) were antigenaemic and anti-p24 core antibody negative before the start of treatment. Changes in antigen concentration after commencing treatment are shown in the figure, anticore antibody concentrations changing in a reciprocal manner. Loss of antigen was sustained in three children, but case 4, who had much more advanced disease on starting treatment, became antigenaemic again nine months into treatment. Three children (cases 3, 5, 6) have been consistently antigen negative, and in one child (case 7) insufficient data was available before the start of treatment, but 12 months after treatment he is core antigen positive (>750 IU/ml).

Treatment was well tolerated in all children. One child developed a brief encephalopathic episode, with aphasia and confusion during one infusion, over a year after commencing treatment. This was attributed to hyperviscosity, and he has had further infusions at a slower rate without incident. No other side effects have been observed.

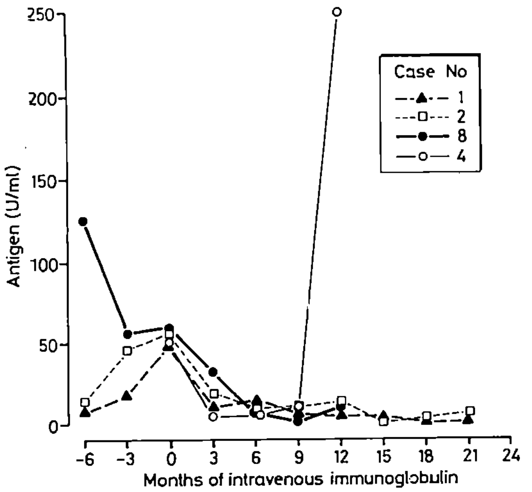

Figure *Sequential antigen concentrations in the four children who were antigenaemic before treatment with intravenous immunoglobulin expressed as Abbott units (positive >20).*

Discussion

Anecdotal evidence of the benefits of intravenous immunoglobulin treatment after short periods of follow up has been reported previously by a number of groups using regimens varying from 200 mg/kg monthly[14] to 300 mg/kg every two weeks. All show reduction in febrile episodes and number of bacterial infections. A more detailed analysis of clinical effect is provided by Schaad *et al*,[20] but the length of follow up was limited to only six months in four of the seven children described. Oleske *et al* in a larger but non-randomised study suggest that mortality is decreased.[14] Calvelli and Rubenstein[13] and Gupta *et al*[21] have also noted changes in T cell and cell mediated immune function in vivo. In all studies, however, interpretation of results is hampered by the small numbers involved and the lack of control data. Because of the limited treatment options, and the small number of children involved in our study, we felt an untreated control group was not appropriate. Because we have followed up these children prospectively from the time of their diagnosis as being HIV positive, however, we have reliable sequential data for a comparable 12 month period immediately before treatment was commenced. This enables us to use each patient before treatment as his own control, given that the natural history of the disease is one of deterioration in the absence of intervention. In addition, no previous group has documented changes in core antigen and antibody concentrations after treatment, nor have the financial implications been assessed.

Our group showed a great deal of heterogeneity in terms of age, duration, and severity of symptoms before treatment, posing difficulties when analysing the cohort as a whole. These were partly overcome by using the patient as his own control, and also, for example, by standardising growth data in terms of velocities. The choice of our dosage regimen aiming to provide the optimum benefit with minimum distress for the child was based upon data from treatment of primary hypogammaglobulinaemia.[16] It is possible, however, that higher doses may be required more frequently in hypergammaglobulinaemic patients, as the half life of immunoglobulin is reduced at higher serum concentrations. This issue of optimal dosage will only be resolved by further studies of efficacy.

Disappearance of core antigen has been described in adults after the infusion of plasma high in anti-p24 antibody and neutralising capacity has been described previously.[22] No studies of normal immunoglobulin treatment have documented changes in core antigen, and in view of the small numbers involved, further studies will be required to verify these findings. The mechanism is likely to be very different, as plasma donors are screened for HIV infection and the intravenous immunoglobulin preparation has no anti-HIV antibody. It has been suggested that the production of HIV antigen is an indicator of enhanced expression of viral genes,[23] and may reflect the expression of latent virus after activation of helper T cells. Bacterial and viral infection increase T cell activation, and the disappearance of p24 antigen after commencing treatment may be due to the reduction of viral activation after the decrease in infective episodes. The continued decline in the T4 count was disappointing, but the disappearance of core antigen with intravenous immunoglobulin treatment suggests that the progression to AIDS may be delayed, as the loss of anti-p24 antibody and the appearance of core antigen are recognised bad prognostic signs.[24]

The clinical benefit of treatment we have shown, together with the quality of life enjoyed by our patients, leads us to conclude (in agreement with Schaad's group[19]) that there is no case for withholding intravenous immunoglobulin treatment in symptomatic children. This precludes a double blind placebo controlled trial at this stage, although further studies may be necessary to optimise the dose regimen. What remains unclear, however, is at what point in the course of disease treatment should be commenced, given that five of our children were in the early stages of symptomatic disease (CDC P2 A/F).[25] A controlled trial will be necessary if we are to consider treatment in asymptomatic children. This is liable to be problematic, however, because at present there is still no reliable diagnostic test of HIV infection in young children. As the problem of HIV infection in children grows over the next few years, routine intravenous immunoglobulin treatment has major implications in budgeting of hospital inpatient and day care facilities. We have shown the cost benefit of treatment—at least in the short and medium term. In is unlikely, however, that intravenous immunoglobulin will delay progression indefinitely, and further advances in immunotherapy, such as the introduction of specific anti-HIV neutralising antibody in combination with intravenous immunoglobulin and anti-retroviral treatment, will be required if we are to improve the ultimate prognosis for HIV infected children.

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References

[1] Scott GB, Buck WE, Leterman JG, *et al.* Acquired immunodeficiency syndrome in infants. *N Engl J Med* 1984;**310**:76–81.

[2] Young LS. Treatable aspects of infection due to human immunodeficiency virus. *Lancet* 1987;**ii**:1503–6.

[3] Fischl MA, Richmann DD, Grieco MH, *et al.* The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS related complex: a double blind, placebo controlled trial. *N Engl J Med* 1987;**317**:185–91.

[4] Minkoff H, Nanda D, Menez R, *et al.* Pregnancies resulting in infants with acquired immunodeficiency syndrome or AIDS related complex: follow-up of mothers, children and subsequently born siblings. *Obstet Gynecol* 1987;**69**:288–9.

[5] Rubenstein A, Sicklick M, Gupta A, *et al.* Acquired immunodeficiency with reverse T4/T8 ratios in infants born to promiscuous and drug-addicted mothers. *JAMA* 1983;**249**:2350–6.

[6] Bernstein LJ, Krieger BZ, Novick B, *et al.* Bacterial infections in the acquired immunodeficiency syndrome of children. *Pediatr Infect Dis* 1985;**4**:472–5.

[7] Bernstein LJ, Ochs HD, Wedgwood RJ, *et al.* Defective humoral immunity in pediatric acquired immune deficiency syndrome. *J Pediatr* 1985;**107**:352–7.

[8] Ammann AJ. The acquired immunodeficiency syndrome in infants and children. *Ann Intern Med* 1985;**103**:734–7.

[9] Maloney MJ, Guill MF, Wray BB, *et al.* Pediatric acquired immune deficiency syndrome with panhypogammaglobulinaemia. *J Pediatr* 1987;**110**:266–7.

[10] Pahwa R, Good RA, Pahwa S. Prematurity, hypogammaglobulinaemia and neuropathology with human immunodeficiency virus (HIV) infection. *Proc Natl Acad Sci USA* 1987;**84**:3826–30.

[11] Espanol T, Garcia-Arumi R, Bofill A, *et al.* Hypogammaglobulinaemia and negative anti-HIV antibodies in AIDS. *Arch Dis Child* 1987;**62**:853–4.

[12] Zolla-Pazner S. Immunologic abnormalities in infection with the human immunodeficiency virus. *Laboratory Medicine* 1986;**17**:685–9.

[13] Calvelli TA, Rubinstein A. Intravenous gammaglobulin in infant acquired immunodeficiency syndrome. *Pediatr Infect Dis* 1986;**5**:S207–10.

[14] Oleske JM, Connor EM, Bohila R, *et al.* The use of IV IgG in children with AIDS. *Vox Sang* 1987;**52**:162–75.

[15] Williams PE, Hague RA, Yap PL, *et al.* Treatment of human immunodeficiency virus antibody positive children with intravenous immunoglobulin. *J Hosp Infect* 1988;**12** (supp D):67–73.

[16] Leen CLS, Yap PL, McClelland DBL. Increase of serum immunoglobulin level into the normal range in primary hypogammaglobulinaemia by dosage individualisation of intravenous immunoglobulin. *Vox Sang* 1986;**51**:278–86.

[17] Mok JYQ, Hague RA, Yap PL, *et al.* The management of children born to HIV seropositive women. *J Infect* 1989;**18**:119–24.

[18] Common Services Agency of the Scottish Health Service. *Scottish health service costs, year ending 31st March 1988.* Edinburgh: Public Treasurer's Department, Lothian Health Board.

[19] Matthes J, Walker LA, Watson JG, *et al.* AIDS encephalopathy with response to treatment. *Arch Dis Child* 1988;**63**:545–7.

[20] Schaad UB, Gianella-Borradori A, Perret B, *et al.* Intravenous immune globulin in symptomatic paediatric human immunodeficiency virus infection. *Eur J Paediatr* 1988;**147**:300–3.

[21] Gupta A, Novick B, Rubinstein A. Restoration of suppressor T-cell functions in children with AIDS following intravenous gamma globulin treatment. *Am J Dis Child* 1986;**140**:143–6.

[22] Jackson GG, Perkins JT, Rubenis M, *et al.* Passive immunoneutralisation of HIV in patients with advanced AIDS. *Lancet* 1988;**ii**:647–52.

[23] Nabel GJ. Activation of human immunodeficiency virus. *J Lab Clin Med* 1988;**111**:495–500.

[24] Lange JMA, Paul DA, Huisman HG, *et al.* Persistent HIV antigenaemia and decline of HIV core antibodies associated with transition to AIDS. *Br Med J* 1986;**293**:1459–62.

[25] Centers for Disease Control. Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR* 1987;**36**:225–30.

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Night blindness and conjunctival xerosis caused by vitamin A deficiency in patients with cystic fibrosis

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SUMMARY Forty three patients with cystic fibrosis, aged 8–44 years (median 16 years), were examined for evidence of vitamin A deficiency. Eight patients had abnormal dark adaptation tests and three had conjunctival xerosis. Serum vitamin A and retinol binding protein concentrations were significantly lower in the affected patients who were also more likely to have abnormal liver function tests. Five patients were treated with 100 000–200 000 IU water miscible vitamin A orally and their daily vitamin supplements were increased to maintain normal concentrations. In four patients dark adaptation tests were repeated. Three were normal, but one patient required three further doses of water miscible vitamin A and a daily supplement of 12 000 IU vitamin A before her dark adaptation threshold returned to normal. Adolescents with cystic fibrosis are liable to develop night blindness and conjunctival xerosis, particularly if they have liver disease or fail to take daily vitamin supplements.

When the pathological features of cystic fibrosis were first described by Andersen there was evidence of vitamin A deficiency in the conjunctivas or respiratory epithelia of 10 of the 44 patients reported.[1] Subsequent studies have shown that despite taking vitamin supplements and pancreatic enzymes to control malabsorption, patients with cystic fibrosis tend to have low serum concentrations of vitamin A.[2 3] Vitamin A is stored in the liver and released bound to retinol binding protein. Normally, serum levels of vitamin A and retinol binding protein reflect the state of liver stores. Some patients with cystic fibrosis, however, have low levels of retinol binding protein and serum vitamin A despite raised concentrations of vitamin A in the liver, which suggests that release of vitamin A from liver stores may be defective.[4 5]

Vitamin A is essential for the synthesis of rhodopsin in the retina, and an early symptom of vitamin A deficiency is night blindness. It is also necessary for the maintenance of secretory epithelia.[6] When vitamin A deficiency is of long standing, keratinising squamous metaplasia of the conjunctiva occurs leading to conjunctival xerosis, and eventually to xerophthalmia with corneal ulceration.

There have been few reports of clinical problems caused by vitamin A deficiency in patients with cystic fibrosis.[7–9] Fulton *et al* investigated dark adaptation in 56 patients with cystic fibrosis and found that mean thresholds were higher in patients than in controls. Two of their patients had night blindness that responded to treatment with water miscible vitamin A.[10] Only 15 patients, however, were able to produce a full dark adaptation curve.

This study was designed firstly to establish the incidence of clinically important vitamin A deficiency in a population of patients old enough to perform a full dark adaptation test, and secondly to determine the optimum treatment for affected patients.

Patients and methods

Fifty two patients attending the cystic fibrosis clinic in Nottingham who were old enough to perform a dark adaptation test were invited to take part in the study. All patients were taking two multivitamin tablets (5000 IU vitamin A and 100–200 mg vitamin E) daily and all except two were taking enteric coated pancreatic enzyme supplements. Four normal adolescents aged 14–16 years acted as controls.

Although it is customary to measure serum vitamin concentrations when patients had fasted, this was not possible because the outpatient clinic was held in the afternoon. Vitamin supplements had been taken before breakfast, at least six hours before blood was taken. Venous blood (5 ml) was taken and kept in the dark and the serum was separated and stored at −70°C until analysis. Vitamins A and E were measured by high performance liquid chromatography and retinol binding protein by an immunodiffusion kit (LC Partigen, Behring). The results of liver function tests carried out within three months of the dark adaptation test were recorded. These included estimations of serum alkaline phosphatase and γ glutamyltransferase activity, and measurements of the concentrations of albumin and bilirubin.

All patients had their visual acuity measured and their eyes were examined with a slit lamp and ophthalmoscope. Thirty one patients performed dark adaptation tests by two methods: a modification of the Friedmann field analyser (measuring total retinal response) and a computer system (measuring point retinal responses to red and green spots of light). In both tests the retina was first bleached by exposure to a bright light. The subject then sat in the dark, and the intensity at which a stimulus was first detected was measured every few minutes. The minimum intensity at which a stimulus could be detected after 30 minutes was called the dark adaptation threshold. If rod vision is impaired, the dark adaptation threshold is raised. Because normal values for log (dark adaptation threshold) measured by the computer system rise slightly with age, the log (dark adaptation threshold) for each patient was expressed as the number of standard deviations from the expected mean for age.[11]

As the computer system was found to be a more sensitive test and was easier for the younger patients to perform, this alone was used for 12 further patients and for the follow up of the abnormal patients.

The first two affected patients to be treated were given standard oil based preparations of vitamin A intramuscularly or orally. In patients with malabsorption, water miscible preparations of the fat soluble vitamins are preferable.[12] Subsequent affected patients were given a single oral dose of 100 000–200 0000 IU water miscible vitamin A palmitate (Arovit, Hoffmann La Roche, supplied for named patients) as recommended by the World Health Organisation.[13] The daily dose of vitamin A was then adjusted according to the serum concentration. Dark adaptation tests were repeated at intervals and further doses of water miscible vitamin A given until the serum vitamin A concentration remained in the normal range and the dark adaptation threshold returned to normal.

Results were analysed by the Student's *t* test, the Mann-Whitney U test, Spearman's rank correlation coefficient and the χ^2 test where appropriate using Oxstat programs (Medstat).

Results

Thirty one of the 52 patients who were eligible for the study attended their first appointment. Twelve patients who failed to attend and who were subsequently found to have serum vitamin A concentrations below the normal range attended a second appointment. The median age of these 43 patients was 16 years (range 8–44) and the median Shwachman score was 60 (range 34–95).[14] Nutritional and respiratory variables are shown in table 1.

All patients had normal visual acuity and normal fundi. Eight patients had dark adaptation thresholds more than two standard deviations above the expected mean using the computer system. Two of

Table 1 *Nutritional and respiratory variables in the 43 patients studied*

	Median	*Range*
Weight (% expected)	85	53–126
Height (% expected)	98	85–110
Weight for height (% expected)	90	70–120
Forced expiratory volume in 1 second (% expected)	54	16–108
Forced vital capacity (% expected)	71	22–100
Chrispin-Norman score	18	2–30
Shwachman score	60	33–95

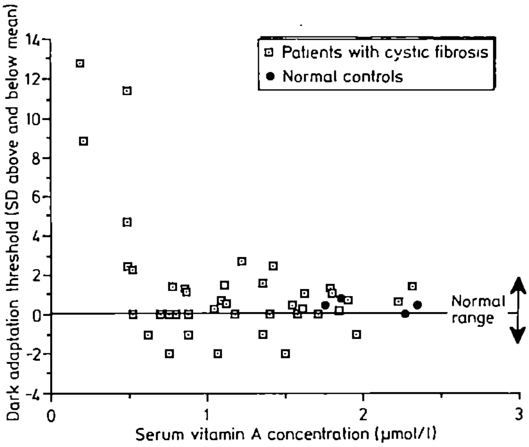

Fig 1 *The association between the dark adaptation threshold (expressed as the number of standard deviations from the expected mean for age) and the serum vitamin A concentrations in 43 patients with cystic fibrosis and four normal controls.*

the eight had normal dark adaptation tests using the Friedmann field analyser and had vitamin A and retinol binding protein concentrations within the normal ranges. The other six all had serum vitamin A concentrations below 0·7 μmol/l and low retinol binding protein concentrations, and four had abnormal Friedmann tests. Four of the six had experienced symptoms of night blindness but had not reported them.

Fig 1 shows the rapid rise in the dark adaptation threshold when the serum vitamin A concentration fell below 0·7 μmol/l. The four normal controls all had dark adaptation thresholds within one standard deviation of the expected mean.

Two of the patients with abnormal dark adaptation, and one other patient, had conjunctival xerosis (as previously reported[15]), so that a total of nine patients had clinical evidence of vitamin A deficiency.

The median (range) serum vitamin A concentration for the 43 patients was reduced at 1·07 μmol/l (0·19–2·3) compared with 2·0 μmol/l (1·76–2·35) for the controls (adult normal range 1·08–7·0 μmol/l) (p=0·0005). The median serum retinol binding protein concentration was 18·7 mg/l (1–46) (adult normal range 30–60 mg/l) and retinol binding protein concentrations were significantly correlated with serum vitamin A concentrations (rs=0·77, p<0·0001). When the nine affected patients were compared with the other 34 patients, serum vitamin A and retinol binding protein concentrations were significantly lower in the affected group (table 2).

The median serum vitamin E concentration for the patients was 12·8 μmol/l (range 4·8–50·4) (adult normal range 17–47 μmol/l) but there was no significant difference between the affected group and the other patients (fig 2). Six of the nine affected patients had abnormal liver function tests, compared with 10 of the 34 unaffected patients (χ^2=4·75, p<0·05). There was no difference between the two groups in age, sex, Shwachman score, lung function, Chrispin-Norman score, or percentage of expected weight for height. Three of the affected patients admitted that they had not taken their vitamins regularly in the past.

Mortality in the affected group was significantly increased (χ^2=5·65, p<0·05). Four affected patients died within two years of the start of the study (one from liver disease and three from chest disease) whereas two of the 34 unaffected patients died from

Table 2 *Serum vitamin A and retinol binding protein concentrations in patients with and without clinical evidence of vitamin A deficiency. Values are expressed as median (range)*

	Abnormal dark adaptation threshold or xerosis (n=9)	*Normal dark adaptation threshold no xerosis (n=34)*	*p Value*
Vitamin A (μmol/l)	0·53 (0·2–1·4)	1·1 (0·5–2·3)	0·002
Retinol binding protein (mg/l)	7·5 (1–31)	26 (4·5–46)	0·016

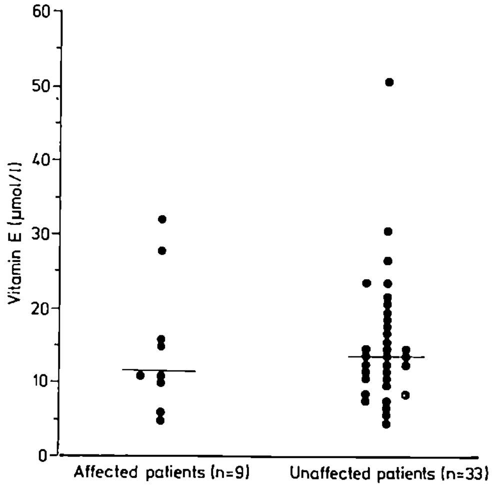

Fig 2 *Serum vitamin E concentrations in affected and unaffected patients with cystic fibrosis. Bars indicate median for each group.*

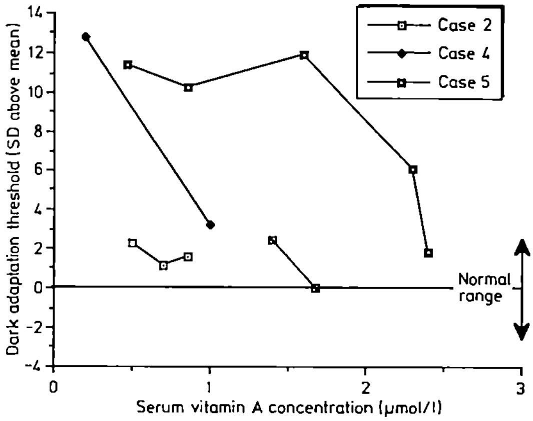

Fig 3 *Improvement in the dark adaptation threshold (expressed as the number of standard deviations above the expected mean for age) and the improvement in the serum vitamin A concentration after treatment in four of the affected patients.*

chest disease, one of these also having distal intestinal obstruction syndrome.

Five patients with abnormal dark adaptation thresholds were each treated with a single oral dose of water miscible vitamin A. In all cases, serum vitamin A concentrations rose into the normal range within a few days, but then gradually fell over the next two months in spite of increased daily vitamin supplements. Four patients were well enough to perform repeat dark adaptation tests (fig 3). The response to treatment was variable, as illustrated by the following case reports.

CASE REPORTS

Case 1

A 15 year old boy developed jaundice and his lung disease deteriorated rapidly. He had gross conjunctival xerosis and abnormal dark adaptation. His serum vitamin A concentration was 0·2 μmol/l and retinol binding protein 1·0 mg/l. His liver function tests were abnormal: serum alkaline phosphatase 1493 IU/l (normal range 80–280), alanine aminotransferase 76 IU/l (normal range 5–40), γ glutamyltransferase 215 IU/l (normal range 10–50), albumin 290 g/l (normal range 300–520), bilirubin 61 μmol/l (normal range 5–17). He was treated with an intramuscular injection of 300 000 IU oil based vitamin A, but after one week his serum vitamin A concentration rose to only 0·3 μmol/l and retinol binding protein fell below 0·1 mg/l. There was no improvement in his conjunctival xerosis. He developed liver failure, and died a few weeks later before the dark adaptation test could be repeated. A liver biopsy specimen taken at necropsy showed cirrhosis.

Cases 2 and 3

Two brothers, aged 8 and 12 years, were found to have conjunctival xerosis. Each had been taking only one multivitamin tablet (2500 IU vitamin A) daily. The younger brother had abnormal dark adaptation, his serum vitamin A concentration was 0·5 μmol/l, and retinol binding protein 9 mg/l. His liver enzyme activities were normal apart from alanine aminotransferase of 60 IU/l. He was treated with 25 000 IU vitamin A daily in a standard oil based preparation for two weeks. Although his serum vitamin A concentration improved and his dark adaptation threshold returned to normal the conjunctival xerosis persisted for a year. He was treated with 100 000 IU water miscible vitamin A orally on two occasions in addition to 8000 IU vitamin A daily. His plasma zinc concentration was 8·2 μmol/l (normal range 11–20 μmol/l) and he was given oral zinc sulphate 220 mg daily for one month, after which the xerosis improved. His older brother also had persistent conjunctival xerosis despite normal vitamin concentrations and normal dark adaptation. His retinol binding protein concentration was 13 mg/l and liver function tests were normal. His plasma zinc concentration was 9·6 μmol/l. He was given oral zinc sulphate 220 mg in addition to 8000 IU vitamin A daily for one month, after which the xerosis resolved.

Case 4

A 15 year old girl, who admitted that she had not been taking her vitamin supplements, had grossly abnormal dark adaptation, a serum vitamin A concentration of 0·2 μmol/l and retinol binding protein of 5 mg/l. Her liver function tests were abnormal: alkaline phosphatase 856 IU/l, alanine aminotransferase 90 IU/l, γ glutamyltransferase 161 IU/l, bilirubin 10 μmol/l, albumin 340 g/l. She was treated with 200 000 IU water miscible vitamin A and then restarted her usual vitamin supplements. Her night blindness rapidly resolved, and two months later her serum vitamin A concentration was 1·0 μmol/l and her dark adaptation test almost normal.

Case 5

A 16 year old girl with severe chest disease and insulin dependent diabetes had grossly abnormal dark adaptation. Her serum vitamin A concentration 9 months previously had been 0·47 μmol/l and retinol binding protein 3 mg/l, although subsequent concentrations were higher. Her liver function tests were normal apart from the serum albumin, which fell to 200 g/l despite overnight nasogastric feeding. Her plasma zinc concentration was 15 μmol/l. She was treated with 200 000 IU water miscible vitamin A orally and her daily supplement of vitamin A was increased to 8000 IU. Her dark adaptation, however, failed to improve. She was therefore given three further doses of water miscible vitamin A and her daily supplement was increased to 12 000 IU. Four weeks later her serum vitamin A level was 2·4 μmol/l. Her dark adaptation threshold returned to normal during the next three months. She died of respiratory failure three months later.

Discussion

In this study clinical evidence of vitamin A deficiency was found in nine out of 43 patients with cystic fibrosis who had been receiving routine vitamin supplementation and pancreatic enzymes. As the patients had been selected by age, and in some cases were already known to have low serum vitamin A concentrations, this is likely to be an overestimate of the overall incidence of vitamin A deficiency.

Nevertheless, night blindness and conjunctival xerosis seem to be surprisingly common in adolescent and young adult patients.

We have confirmed that serum vitamin A, vitamin E, and retinol binding protein concentrations are low in patients with cystic fibrosis, and that the dark adaptation threshold rises rapidly below a serum vitamin A concentration of 0·7 µmol/l, as described by Fulton *et al.*[10] Affected patients are more likely to have low retinol binding protein concentrations and abnormal liver function tests than unaffected patients. The finding of low retinol binding protein concentrations suggests that synthesis and release of retinol binding protein from the liver are deficient. This may explain why some patients responded poorly to treatment with additional vitamin A, because the delivery of vitamin A to the retina is dependent on adequate circulating levels of retinol binding protein. This is illustrated by cases 1 and 5.

Vitamin E supplementation improves serum vitamin A concentrations, although the reason for this is not known.[16] All our patients were prescribed vitamin E supplements, but their serum concentrations were low, suggesting either that the dose prescribed was inadequate or that compliance was poor.

In patients with xerosis or night blindness who fail to respond to additional vitamin A supplements despite achieving normal serum vitamin A concentrations, the possibility of zinc deficiency should be considered. Zinc is required for the release of vitamin A and retinol binding protein from liver stores, and acts as a coenzyme for retinol dehydrogenase in the retina.[17] In two patients in this study (cases 2 and 3) xerosis resolved with zinc supplementation.

Three of the affected patients had severe lung disease and have since died. It is interesting to speculate what effect vitamin A deficiency may have had on the lung disease. Deficiency is known to cause squamous metaplasia of respiratory epithelia, and may predispose to infection.[18] It has been suggested that vitamin A supplementation in premature babies may reduce the incidence of bronchopulmonary dysplasia.[19] Long term studies are required to establish any influence of vitamin A on the progression of lung disease in cystic fibrosis.

We recommend that patients with cystic fibrosis are screened for vitamin A deficiency annually. Serum vitamin A and retinol binding protein concentrations should be measured and those with serum vitamin A below 1 µmol/l should have a full ophthalmological assessment. Conjunctival impression cytology may better reflect vitamin A deficiency over a period of time than a single serum vitamin A measurement, and we are developing this technique for patients who are unable to perform dark adaptation tests.[20]

Some patients require up to 12 000 IU vitamin A and 200 mg vitamin E daily in order to maintain normal serum concentrations. Not taking vitamin supplements was a factor in at least three patients. The treatment of established vitamin A deficiency with a single oral dose of water miscible vitamin A avoids problems with compliance and seems to be effective in most patients. Provided that serum vitamin A levels are monitored, the development of hypervitaminosis A is unlikely. At present, a water miscible preparation of vitamin A is not available for routine prescription in the United Kingdom.

As more patients with cystic fibrosis are reaching the age of 17 years and learning to drive, the detection and prompt treatment of night blindness has become especially important.

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References

[1] Anderson DH. Cystic fibrosis of the pancreas, vitamin A deficiency and bronchiectasis. *J Pediatr* 1939;**15:**763–71.

[2] Congden PJ, Bruce G, Rothburn MM, *et al.* Vitamin status in treated patients with cystic fibrosis. *Arch Dis Child* 1981;**56:** 708–14.

[3] Underwood BA. The determination of vitamin A and some aspects of its distribution, mobilization and transport in health and disease. *World Rev Nutr Diet* 1974;**19:**123–72.

[4] Underwood BA, Denning CR. Blood and liver concentrations of vitamins A and E in children with cystic fibrosis. *Pediatr Res* 1972;**6:**26–31.

[5] Rees-Smith F, Underwood BA, Denning CR, Varma A, Goodman DS. Depressed plasma retinol binding protein levels in cystic fibrosis. *J Lab Clin Med* 1972;**80:**423–33.

[6] Wolf G. Multiple functions of vitamin A. *Physiol Rev* 1984;**64:** 873–937.

[7] Petersen RA, Petersen VS, Robb RM. Vitamin A deficiency with xerophthalmia and night blindness in cystic fibrosis. *Am J Dis Child* 1968;**116:**662.

[8] Abernathy RS. Bulging fontanelle as presenting sign in cystic fibrosis. Vitamin A metabolism and effect on CSF pressure. *Am J Dis Child* 1976;**130:**1360–2.

[9] O'Donnell M, Talbot JF. Vitamin A deficiency in treated cystic fibrosis: case report. *Br J Ophthalmol* 1987;**71:**787–90.

[10] Fulton AB, Hansen RM, Underwood BA, Shwachman H, Barg DC. Scotopic thresholds and plasma retinol in cystic fibrosis. *Invest Ophthalmol Vis Sci* 1982;**23:**364–70.

[11] Neugebauer MAZ, Vernon SA, Brimlow G, Tyrrell JC, Hiller EJ, Marenah C. Nyctalopia and conjunctival xerosis indicating vitamin A deficiency in cystic fibrosis. *Eye* 1989 (in press).

[12] Chase HP, Long MA, Lavin MH. Cystic fibrosis and malnutrition. *J Pediatr* 1979;**95:**337–47.

[13] Stewart-Truswell A. Malnutrition in the Third World—II. *Br Med J* 1985;**291:**587–8.

[14] Shwachman H, Kulczycki LL. Longterm study of 105 patients with cystic fibrosis. *Am J Dis Child* 1958;**96:**6–15.

[15] Vernon SA, Neugebauer MAZ, Brimlow G, Tyrrell JC, Hiller

EJ. Conjunctival xerosis in cystic fibrosis. *J R Soc Med* 1989;**82**:46–7.

[16] Ekvall S, Mitchell A. The effect of supplemental vitamin E on vitamin A serum levels in cystic fibrosis. *Int J Vitam Nutr Res* 1978;**48**:325–32.

[17] Solomons NW, Russell RM. The interaction of vitamin A and zinc: implications for human nutrition. *Am J Clin Nutr* 1980;**33**: 2031–40.

[18] Chandra RK. Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. *Br Med J* 1988;**297**:834–5.

[19] Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr* 1987;**111**:269–77.

[20] Tseng SCS. Staging of conjunctival squamous metaplasia by impression cytology. *Ophthalmology* 1985;**92**:728–33.

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Rise and fall of coeliac disease 1960–85

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SUMMARY A total of 192 children who presented with coeliac disease to Queen Elizabeth Hospital for Children from 1960–85 were reviewed in order to investigate the frequency and the age of presentation. There was a clear peak in the number of children presenting from 1971–5, and although the numbers declined subsequently they have remained at a level similar to numbers found before 1971. There was no difference in the mode of presentation but there was a definite increase in the age of presentation over the time period reviewed. Breast fed babies presented later than bottle fed babies (14 compared with 9 months) despite a similar age of gluten introduction. Similarly bottle fed babies and breast fed babies presented later after 1975 (10·5 compared with 7 months, and 18 compared with 9·5 months, respectively). Before 1975 the median age of gluten introduction was significantly less than that after 1975 (2 compared with 4 months) and the age of gluten introduction correlated with the age of presentation. It is concluded that breast feeding and the age of gluten introduction may influence the age of presentation of childhood coeliac disease but no clear reasons for the rise in incidence in the 1970s have been determined. It does not appear that the disease is declining, however, in recent years children have tended to present later in life.

Recent studies in the United Kingdom have suggested a decline in the numbers of children presenting with coeliac disease since 1972.[1–3] This decrease in numbers may be due to stricter diagnostic criteria, to differences in infant feeding practices, or to other environmental factors such as a decrease in the incidence of acute gastroenteritis in infancy.[4]

In 1974 the Department of Health and Social Security (DHSS) encouraged breast feeding and the later introduction of gluten into the diet in infancy.[5] In order to establish whether these recommendations were associated with any change in feeding patterns and to investigate the frequency and presentation of childhood coeliac disease all children diagnosed with coeliac disease who presented to Queen Elizabeth Hospital for Children from 1960–85 were reviewed.

Patients and methods

A retrospective study was performed of all children with coeliac disease who were diagnosed between 1960 and 1985 at Queen Elizabeth Hospital for Children. Children were included if they fulfilled (1) the diagnostic criteria proposed by the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)[6] or (2) part of the ESPGAN criteria. These children included (a) those who were already on a gluten free diet but who were only included if they had a subsequent positive gluten challenge (that is, a histological relapse on gluten with or without clinical symptoms) or, (b) those who were over 2 years with an abnormal proximal small intestinal biopsy specimen consistent with coeliac disease who responded clinically to a gluten free diet but who were awaiting confirmation of the diagnosis by gluten challenge.

A computerised data base was compiled for each patient detailing age and mode of presentation, dietary history, ethnic origins, and laboratory findings. Breast feeding was defined as any infant who was breast fed regardless of how short a time this was and this was not necessarily exclusive. For purposes of analysis, where the information was available, it was divided into those fed for one month or less, for one to six months, and for greater than six months. Children who were bottle fed had never been breast fed.

Results

A total of 218 children were provisionally diagnosed as having coeliac disease from 1960–85. Twenty six were subsequently shown to have transient gluten intolerance and were not included in the study. Of the remaining 192, 81 fulfilled ESPGAN criteria, 37 had a positive gluten challenge, and 74 had a single abnormal biopsy specimen. One hundred and seventeen (90%) of 130 children were white (15% of whom were of Irish origin), four (3%) were Asian, and the remaining nine (7%) were of mixed races. Data was not available on the other 62 children.

Most children presented in a classical manner with diarrhoea, failure to thrive, abdominal distension, and buttock wasting; 18 (17%) presented with anaemia (table 1). There was no noticeable difference in the mode of presentation with time. Seven children presented with delayed bone age and one child with rickets.

FREQUENCY OF DIAGNOSIS

Examination of the numbers of children diagnosed at this hospital each year showed a small peak of cases in the early 1960s (fig 1). This represented confirmation of clinical diagnosis by small intestinal biopsy, which was introduced at that time. In the early 1970s there was a larger peak that diminished after 1975, although numbers remained at a similar level to those found before the 1970s. The observed peak (1972–5) was significantly different from the expected frequency of diagnosis at that time period and from the observed frequencies for the other years (χ^2 test $p<0{\cdot}001$). Consideration of these patients by year of birth showed a similar peak in the early 1970s (fig 2) with numbers reducing subsequently to a pre-1971 level. In 1985, no child under 2 years was diagnosed as having coeliac disease.

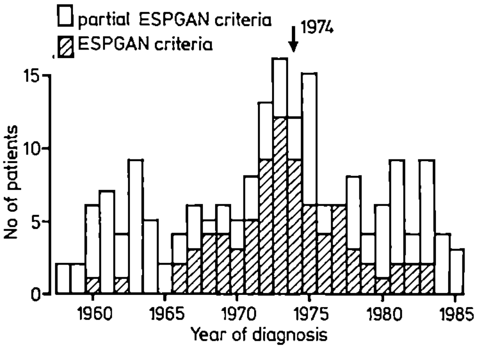

Fig 1 *Year of diagnosis of 192 children with coeliac disease at Queen Elizabeth Hospital 1960–85. (From Diseases of the Small Intestine in Childhood. Third edition, 1988. By J A Walker-Smith. Reproduced with permission of Butterworth Scientific Ltd.)*

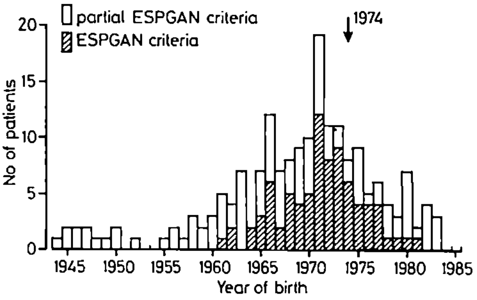

Fig 2 *Year of birth of 192 children with coeliac disease at Queen Elizabeth Hospital 1960–85. (From Diseases of the Small Intestine in Childhood. Third edition, 1988. By J A Walker-Smith. Reproduced with permission of Butterworth Scientific Ltd.)*

Table 1 *Clinical features of childhood coeliac disease at Queen Elizabeth Hospital 1960–85*

	No (%) of children
Presenting symptoms (n=192):	
Diarrhoea	125 (65)
Failure to thrive	98 (51)
Weight <3rd centile	61 (32)
Height <3rd centile	28 (14)
Vomiting	69 (36)
Anorexia	62 (32)
Presenting signs (n=192):	
Abdominal distension	103 (54)
Wasting	72 (37)
Anaemia* (n=108):	18 (17)

*Haemoglobin concentration <90 g/l.

Examination of the mean age of presentation per year of diagnosis showed variation from year to year (fig 3). The overall mean age of presentation was 24 months. In comparison, using the χ^2 test, the mean age in the first seven years (1965–71) was significantly lower (mean=10 months, $p=<0{\cdot}01$) and the mean age in the last seven years (1979–85) was higher (mean=38 months, $p<0{\cdot}05$). The mean age in the middle seven years (1972–78) was not different to the overall mean (mean=23 months, $p>0{\cdot}05$). Thus there was a significant increase in the age of presentation over the 21 years under study.

AGE OF GLUTEN INTRODUCTION

Although there was a clear trend towards a later introduction of gluten over the period under study, and this correlated with later age of presentation (Spearman's correlation coefficient r_s=0·74, p<0·001), there was no significant difference when comparing the overall mean (3·5 months) with the mean in the first seven years (1965–71, mean=2·4 months) or the last seven years (1979–85, mean=5·1 months) by χ^2 test (fig 3). It is apparent that the trend towards a later introduction of gluten into the diet began before the DHSS recommendation.

BREAST AND BOTTLE FEEDING (TABLE 2)

Overall 46% (55/120) of patients were breast fed. Their median age of presentation was 14 months (range 1–180 months). Bottle fed patients presented at the earlier age of 9 months (range 1–84 months, p=0·01, Mann-Whitney U test). There was no difference in the age of gluten introduction between the two groups. It was apparent that the median age of presentation increased with length of breast feeding (<1 compared with 1–6 months: p=0·05; 1–6 compared with >6 months: p=0·05), although there was no difference in the age of gluten introduction.

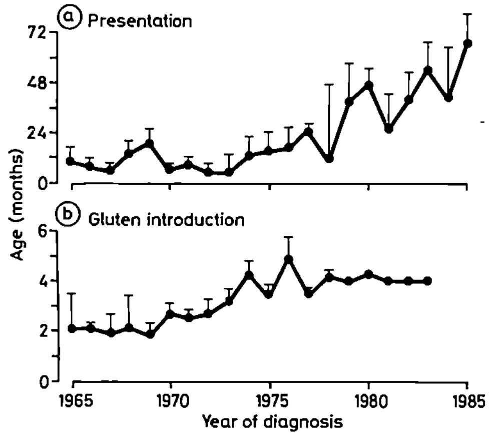

Fig 3 *Age of presentation and age of gluten introduction per year of diagnosis.*

Dividing the patients into breast and bottle fed groups before and after 1975 (the date of the DHSS recommendation to delay gluten introduction) showed, in both groups, an increase in the median age of presentation (breast fed p=0·004, bottle fed p=0·006) and in the time of gluten introduction after 1974 (p=0·02) (Mann-Whitney U test).

ASSOCIATION OF COELIAC DISEASE TO ACUTE GASTROENTERITIS

Admissions of children with acute gastroenteritis from 1960–85 increased slightly up to 1973, they

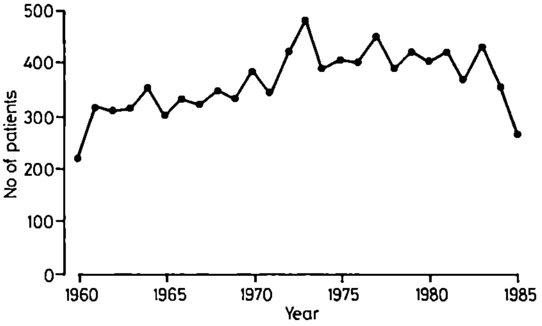

Fig 4 *Number of children admitted to Queen Elizabeth Hospital with acute gastroenteritis 1960–85.*

Table 2 *Breast and bottle feeding: age of presentation and introduction of gluten*

	No of children	*Median age of gluten introduction (range)*	*Median age of presentation (range)*
Overall:			
Breast fed	55	4·0 (0·1–24·0)	14 (1–180)
Bottle fed	65	3·0 (0·1–7·0)	9 (1–84)
Before 1975:			
Breast fed	24	2·0 (0·1–6·0)	9·5 (1–164)
Bottle fed	39	2·0 (0·1–6·0)	7·0 (1–72)
After (and including) 1975:			
Breast fed	31	4·0 (10·0–24·0)	18·0 (3–180)
Bottle fed	26	4·0 (1·0–7·0)	10·5 (2–84)
Length of breast feeding (months):			
<1	24	3·0 (0·0–5·0)	11·5 (1·0–6·0)
1–6	18	4·0 (1·2–6·0)	16·5 (40–164)
>6	8	4·0 (4–24)	41·0 (16–136)

remained constant to 1983, and declined subsequently (fig 4).

Discussion

The numbers of children diagnosed with coeliac disease at Queen Elizabeth Hospital for Children increased slowly up to the early 1970s, peaked between 1971 and 1975, and gradually declined to levels found before 1971. The observed frequency of diagnosis would not have been found if the incidence of coeliac disease had been constant from year to year, implying that a significant change in incidence occurred from 1971–5.

Although this is not an epidemiological study, it does represent the referral pattern of an east London hospital with a catchment mainly from east London, Essex, and west Kent. Over the time period of the study there has been a specialist interest in coeliac disease throughout and small intestinal biopsies have been performed since 1958. Other recent studies that have commented on the decline of childhood coeliac disease[1–3] did not discuss the rise in the early 1970s that has been noted in both children and adults[7]; this is perhaps because, unlike the studies at our hospital, there was insufficient data collected before 1970. Evaluation of the two peaks of presentation in this study suggest that the minor peak (1960–3) represented histological confirmation of earlier clinical diagnoses; the major peak (1971–4), however, may possibly have been due to increased referral or due to a change in the pattern of infant feeding.

In this study both bottle feeding and early gluten introduction were associated with an earlier presentation as previously suggested,[8–10] and may have been associated with the documented rise. On the other hand breast fed babies presented later (table 2), and this data supports other studies, which have described a delaying effect of breast feeding on the age of presentation of coeliac disease.[10–12] It is possible that this may have been associated with better infant hygiene and a decline in infantile gastroenteritis.[4] The data do not support this, however, as the numbers of children admitted with acute gastroenteritis over the 25 year period gradually increased up to 1983. The subsequent decline is probably related to better community education and the care of children as outpatients.

In conclusion, the numbers of children diagnosed with coeliac disease rose in the early 1970s, although the reasons for this have not been established by this study. The subsequent decrease in numbers may be associated with differences in infant feeding in infancy which may cause increasingly later presentation rather than an overall decline in disease incidence.

References

[1] Littlewood JM, Crollick AJ, Richards IDG. Childhood coeliac disease is disappearing. *Lancet* 1980;**ii**:1359.

[2] Challacombe DN, Bayliss JM. Childhood coeliac disease is disappearing. *Lancet* 1980;**ii**:1360.

[3] Dossetor JFB, Gibson AAM, McNeish AS. Childhood coeliac disease is disappearing. *Lancet* 1981;**1**:322–3.

[4] Challacombe DN. The incidence of coeliac disease and early weaning. *Arch Dis Child* 1983;**58**:326.

[5] Panel on Child Nutrition Working Party on Infant Feeding. *Present-day practice in infant feeding*. Report on health and social subjects No 9. London: HMSO, 1974:24–6.

[6] Meeuwisse GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59**:461–3.

[7] Langman MJS, McConwell TH, Sigelhalter DJ, McConwell RB. Changing patterns of coeliac disease frequency: an analysis of coeliac society membership records. *Gut* 1985;**26**:275–8.

[8] Arneil GC. *Dietary study of 4365 Scottish infants—1965*. Scottish Health Service Studies No 6. Edinburgh: HMSO, 1967:89.

[9] Anderson CM, Gracey M, Burke V. Coeliac disease. Some still controversial aspects. *Arch Dis Child* 1972;**47**:292–8.

[10] Auricchio S, Follo D, de Ritis G, Marubini E. Does breast feeding protect against the development of clinical symptoms of coeliac disease in children. *J Pediatr Gastroenterol Nutr* 1983;**2**: 428–33.

[11] Polancoe I, Vasquez C, Prieto G, *et al.* Coeliac disease (CD): influence of breast feeding (BF) and HLA-DR phenotypes on the age of onset of symptoms. *Pediatr Res* 1982;**16**:1044.

[12] Pittard WB. Breast milk immunology. A frontier in infant nutrition. *Am J Dis Child* 1979;**133**:83–7.

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Diarrhoea in jaundiced neonates treated with phototherapy: role of intestinal secretion

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SUMMARY Thirty jaundiced neonates with diarrhoea who were being treated with phototherapy and 30 matched control infants were studied to try and find out the cause of the diarrhoea. Faecal osmolality and electrolyte concentrations were measured, which gave clear evidence that the diarrhoea arose from intestinal secretion. Rectal water and electrolyte absorption in 10 jaundiced infants receiving phototherapy, in 10 jaundiced infants not receiving phototherapy, and in 10 healthy controls was measured with a rectal dialysis bag. A further group of eight jaundiced infants was also studied both during and after phototherapy to document the reversal of ion transport changes. Absorption of water, sodium chloride, and potassium was significantly impaired in the patients receiving phototherapy compared with each of the control groups. Such impairment was transient, as it was not apparent when the jaundice faded and phototherapy was stopped. These data show that the colon plays a part in the pathogenesis of secretory diarrhoea and that both hyperbilirubinaemia and phototherapy are necessary for such an effect to develop.

Since Cremer introduced phototherapy for the treatment of neonatal jaundice, the presence of watery and greenish stools has often been reported in neonates receiving phototherapy.[1] The pathogenesis of this complication is unclear. In 1977, Bakken reported a temporary lactase deficiency in six jaundiced infants treated in this way, which he attributed to the mucosal injury[2]; this finding was not confirmed, later on, by Ebbesen nor, more recently, by Bujanover *et al.*[3–5]

On the basis of the results of measurement of stool electrolytes and osmolality in 10 jaundiced babies receiving phototherapy, we suggested that the diarrhoea might be secretory.[6] In the present report we extend those preliminary observations and present evidence of secretory changes induced by phototherapy in the distal colon of babies—that is, the only segment of the gastrointestinal tract that we consider it ethical to investigate in newborn infants.

Patients and methods

We measured faecal osmolality and electrolyte concentrations in 30 newborn infants with uncomplicated hyperbilirubinaemia (mean (SEM) serum bilirubin 265 (3·4) μmol/l) who had diarrhoea when exposed to blue light at 650–700 μW/cm^2 and in 30 healthy newborn infants who had neither jaundice nor diarrhoea.

There were no significant differences in mean (SEM) birth weight (3462 (88) and 3526 (109) g), gestational age (39·3 (0·3) and 39·4 (0·3) weeks), postnatal age at beginning of the study (76 (2) and 64 (2) hours) between the two groups. All infants were breast fed, and feeding regimens were the same in both groups. Hyperbilirubinaemic infants had a mean bilirubin concentration at the time of the study of 274 (17) μmol/l and received phototherapy for 16 (2) hours.

In a separate series of experiments we studied the absorption of electrolytes in the rectum by a modification of the non-equilibrium dialysis method of Edmonds and Godfrey[7 8] in 10 jaundiced infants with diarrhoea receiving phototherapy, 10 jaundiced infants not receiving phototherapy, and 10 healthy controls. The groups were well matched for birth weight, gestational age, and age at the beginning of the study (table 1). Mean (SEM) serum bilirubin concentration at the study was 257 (5) μmol/l in the group treated with phototherapy and 238 (3) μmol/l in the group not so treated; it was 94 (7) μmol/l in the group that was not jaundiced. Phototherapy was given for 18 (3) hours.

In addition, to obtain direct evidence that electrolyte transport changes were associated with photo-

Table 1 *Details of infants studied. Values are expressed as mean (SEM)*

	Birth weight (g)	*Gestational age (weeks)*	*Age at beginning of study (hours)*
Jaundiced infants receiving phototherapy (n=10)	3402 (95)	38·9 (0·2)	88 (3)
Jaundiced infants not receiving phototherapy (n=10)	3368 (146)	39·6 (0·3)	86 (3)
Infants not jaundiced (n=10)	3547 (67)	39·2 (0·4)	83 (3)

therapy, we investigated eight breast fed newborn infants both during phototherapy and after they had completed it. They had a mean (SEM) birth weight of 3360 (158) g and gestational age of 39·0 (0·6) weeks. They were investigated with the dialysis technique at 85 (5) hours of life while receiving phototherapy, and their mean serum bilirubin concentration was 274 (7) μmol/l. They were then reexamined when they were 129 (5) hours old after phototherapy had been discontinued, and the concentration had dropped to 178 (9) μmol/l.

The experimental technique consisted of insertion into the rectum of a weighed dialysis bag (5·3 cm^2) made from visking tube and mounted on a 6F gauge nasogastric tube. The bag was filled with an isotonic electrolyte solution containing sodium 140 mmol/l, potassium 20 mmol/l, chloride 130 mmol/l, and bicarbonate 30 mmol/l. After being positioned the bag was left in situ for 30 minutes and then removed and reweighed. The sodium and potassium concentrations were measured by flame photometry and chloride by a chloridometer. The observed changes in weight and in electrolyte content were finally calculated and assumed to represent net fluxes (either absorptive or secretory) of water and electrolytes, respectively.

Table 2 *Stool osmolality and electrolyte concentrations. Values are expressed as mean (SEM)*

	Jaundiced infants receiving phototherapy (n=30)	*Healthy infants (n=30)*	*p Value*
Stool osmolality (mOsm/l)	269 (10)	284 (13)	>0·1
Sodium (mmol/l)	63 (4)	38 (6)	<0·001
Potassium (mmol/l)	52 (3)	31 (5)	<0·001
Anion gap (mmol/l)	37 (4)	144 (17)	<0·001

Values are expressed as mean (SEM). The significance of the differences was calculated by Student's *t* test for either paired or unpaired variables, as appropriate. Informed consent was obtained from all the parents.

Results

Table 2 shows the mean (SEM) values of stool osmolality and electrolytes in the 30 jaundiced infants with diarrhoea who were receiving phototherapy, and in the 30 healthy controls. The data on electrolyte concentration and the anion gap are consistent with a secretory pattern for the diarrhoea.

Table 3 shows the net absorption of water and electrolytes in the 10 jaundiced infants with diarrhoea who were receiving phototherapy, in the 10 jaundiced infants not receiving phototherapy, and in the 10 healthy control infants. A clear inhibition of absorption of water and electrolytes was seen in jaundiced infants receiving phototherapy. Such inhibition is highly significant in comparison with each of the two control groups (the jaundiced infants not receiving phototherapy and the healthy infants).

Table 4 shows the net absorption of water and electrolytes in the eight infants who were studied during and after phototherapy. It is evident that the inhibition of water and electrolyte absorption found during phototherapy completely disappeared after it had been stopped, and the jaundice had regressed.

Table 3 *Rectal net absorption of water and electrolytes. Values are expressed as mean (SEM)*

	Jaundiced infants receiving phototherapy (n=10)	*p Value*	*Jaundiced neonates not receiving phototherapy (n=10)*	*p Value*	*Neonates not jaundiced (n=10)*
Water (μl/min/cm^2)	2·1 (0·04)*	<0·01	3·6 (0·006)	>0·05	3·3 (0·09)
Sodium (μmol/min/cm^2)	286 (8)*	<0·01	357 (8)	>0·05	331 (10)
Chloride (μmol/min/cm^2)	291 (11)*	<0·01	500 (11)	<0·01	358 (13)
Potassium (μmol/min/cm^2)	3 (3)*	<0·01	69 (2)	>0·05	58 (6)

*p<0·01 when compared with neonates not jaundiced.

Table 4 *Net absorption of water and electrolytes during and after phototherapy. Values are expressed as mean (SEM)*

	Water ($\mu l/min/cm^2$)	*Sodium ($\mu mol/min/cm^2$)*	*Chloride ($\mu mol/min/cm^2$)*	*Potassium ($\mu mol/min/cm^2$)*
During phototherapy	2·6 (0·1)	248 (8)	266 (8)	6 (1)
After phototherapy	3·6 (0·2)	308 (9)	329 (11)	13 (3)
p Value	<0·001	<0·01	<0·01	=0·016

Discussion

The aim of our work was twofold: to extend and confirm our preliminary report that had suggested the secretory nature of the diarrhoea found in jaundiced infants receiving phototherapy,[6] and to verify whether secretory changes could be found in an intestinal segment as supporting evidence for such a mechanism.

The data reported here in 60 more infants both confirm our earlier observations on the changes in stool electrolytes and osmolality in jaundiced neonates receiving phototherapy, and set reference values for such measurements in breast fed neonates born at full term. The observation of normal osmolality and of a small anion gap in the faeces of the study group permits the ruling out of the presence of osmotically active substances, and thus according to Krejis and Fordtran,[9] the pathogenetic mechanism of the diarrhoea can be traced to intestinal secretion. In this respect the rather large value for the anion gap found in the stools of normal babies needs to be commented upon.

Osmotically active solutes in the faeces of breast fed infants are likely to be represented by digestive break down products that are not absorbed. In such neonates, particularly during the first week of life, substantial amounts of reducing substances are lost in the stools. It has also been shown that oligosaccharides, which appear in comparatively high concentrations in human colostrum and milk (24 and 12 g/l, respectively) are poorly absorbed.[10 11]

We chose to evaluate water and electrolyte transport in the rectum with the dialysis method, as no other method was, in our view, sufficiently non-invasive to be used in healthy infants. The results we obtained show a pronounced impairment of absorptive rates of water and ions in jaundiced infants receiving phototherapy, compared with both jaundiced infants not so treated and the healthy control infants. Furthermore, the reversal of such alterations observed in the same babies after the jaundice had faded and the phototherapy been stopped provides compelling evidence that the anti-absorptive changes are indeed related to jaundice and phototherapy.

Although we did not actually observe secretion, diarrhoea may arise from simple impairment of absorption, which may be sufficient in itself to reverse the overall net water balance.[9] Furthermore, it is possible that the shift towards secretion that we found in the rectum is also present and in greater magnitude in more proximal segments, including the small bowel, which we did not investigate.

As the antiabsorptive effect was seen only in the jaundiced infants receiving phototherapy, and the effect disappeared after regression of the jaundice and stopping the phototherapy, it must be caused by the simultaneous action of hyperbilirubinaemia and phototherapy. These data confirm those of Rubaltelli and Largajalli in 1973 who showed a reduced transit time (which can well be attributed to the increase in the fluidity of intestinal contents) only in jaundiced infants receiving phototherapy and not in those who were not jaundiced and receiving phototherapy or healthy infants receiving no treatment.[12]

Finally, the present data show that jaundiced infants receiving phototherapy develop diarrhoea because of an induced secretory change in net intestinal ion transport. What then are the mechanisms responsible for it? We have shown that the bile from jaundiced, photoirradiated Gunn rats has an antiabsorptive effect in the rat jejunum in vivo.[13] Among the substances that are present in such bile is unconjugated bilirubin in large amounts, and we[13] and others[14] have shown that unconjugated bilirubin is an intestinal secretagogue. Thus although we did not investigate the potential role of other compounds found in bile (such as bile acids or other photo products of bilirubin) we can assume that unconjugated bilirubin is, at least in part, responsible for the observed effect on ion and water transport.

References

1 Jhon E. Complication of phototherapy in neonatal hyperbilirubinemia. *Aust Paediatr J* 1975;**11**:53–5.
2 Bakken AF. Temporary intestinal lactase deficiency in light-treated jaundiced infants. *Acta Paediatr Scand* 1977;**66**:91–6.
3 Ebbesen F. Gut transit time and lactose malabsorption during phototherapy. I. *Acta Paediatr Scand* 1980;**69**:65–8.
4 Ebbesen F. Gut transit time and lactose malabsorption during phototherapy. II. *Acta Paediatr Scand* 1980;**69**:69–71.

[5] Bujanover Y, Schwartz G, Milbaner B, Peled Y. Lactose malabsorption is not a cause of diarrhea during phototherapy. *J Pediatr Gastroenterol Nutr* 1985;4:196–8.

[6] De Curtis M, Saitta F, Matteoli M, Paludetto R, Ciccimarra F, Guandalini S. Evidence for secretory type diarrhea in infants treated by phototherapy. *Lancet* 1982;**i**:909–10.

[7] Edmonds LJ, Godfrey R. Measurement of electrical potentials of the human rectum and pelvic colon in normal and aldosterone treated patients. *Gut* 1970;**11**:330–7.

[8] Savage MO, Jefferson IG, Dillon MJ, Milla PJ, Honour JW, Grand DB. Pseudo hypoaldosteronism: severe salt wasting in infancy caused by generalized mineralcorticoid unresponsiveness. *J Pediatr* 1982;**101**:239–42.

[9] Krejis GJ, Fordtran JS. Diarrhea. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal diseases.* Philadelphia: WB Saunders, 1983:257–80.

[10] Blanc B. Biochemical aspects of human milk comparison with bovine milk. *World Rev Nutr Diet* 1981;**36**:1–39.

[11] De Curtis M, Senterre J, Rigo J, Putet G. Carbohydrate-derived energy absorption in preterm infants fed human milk or formula. *Arch Dis Child* 1986;**61**:867–70.

[12] Rubaltelli FF, Largajolli G. Effects of light exposure on gut transit time in jaundiced newborns. *Biol Neonate* 1973;**62**:146–8.

[13] Guandalini S, Fasano A, Albini F, *et al.* Unconjugated bilirubin and the bile from light-exposed Gunn rats inhibit intestinal water and electrolyte absorption. *Gut* 1988;**29**:366.

[14] Whitington PF, Olsen WA, Odell GB. The effect of bilirubin on the function of hamster small intestine. *Pediatr Res* 1981;**15**: 1009–14.

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Serological and histological follow up of chronic hepatitis B infection

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SUMMARY In order to study the clinical, serological, and morphological evolution of chronic hepatitis B virus infection in childhood, a prospective study has been carried out. A total of 90 children with a chronic infection were followed up for a mean (SD) of 3 (1·8) years. At the beginning of the study, 61 children were asymptomatic and 77 were household contacts of chronic carriers. Serologically 77 were hepatitis B e antigen (HBeAg) positive and 71 of them were positive to hepatitis B virus DNA. The mean alanine aminotransferase activities were higher among HBeAg positive patients than in antihepatitis B e (anti-HBe) positive ones. The most severe histological damage was also found among HBeAg positive patients. The annual seroconversion rate was 14%. A significant increase in the alanine aminotransferase activity was observed 13 (5·6) months before appearance of anti-HBe in the 85% of cases. Among anti-HBe positive patients, the alanine aminotransferase activities were normal in all except three (19%), two of whom had intrahepatic delta antigen. An increase in the histological activity was observed among patients who maintained HBeAg presence while an amelioration of liver damage was observed in anti-HBe carriers.

Chronic hepatitis B virus infection has two distinguishable phases. During the first phase there are circulating Dane particles, hepatitis B e antigen (HBeAg) and hepatitis B virus DNA (HBV–DNA). Usually there is biochemical or pathological evidence of disease activity, or both. Later, either spontaneously or with antiviral treatment, those particles disappear from the circulation, HBeAg and HBV–DNA become undetectable, and antihepatitis B e (anti-HBe) develops.[1]

Several reports on the natural history of chronic hepatitis B infection in children have been published with differing results.[2–8] Cirrhosis has been reported in 3%[7] to 25%.[4 5] Because of these varying findings we have carried out a prospective study in children with chronic hepatitis B virus infection.

Patients and methods

Our study comprised 134 children who were positive carriers for hepatitis B and who attended our hospital from 1979 to 1986; 44 were not available for long term follow up. We studied the remaining 90 children: all were hepatitis B surface antigen (HBsAg) and antihepatitis B c (anti-HBc) positive with raised alanine aminotransferase activities for at least six months and were available for long term follow up. Other causes of liver disease were ruled out (α_1 antitrypsin deficiency, Wilson's disease, autoimmune chronic hepatitis, etc). The clinical, serological, and biochemical features are summarised in table 1. The children ranged from 6 months to 14 years of age (mean (SD) 6 (3) years). There were 55 boys and 35 girls. A clinical and serological follow up (every four months) was performed during a mean of three years (range six months to seven years). At the beginning of the study, 29 (32%) children had one or more of the following clinical symptoms of liver disease: asthenia (n=14, 15%), anorexia (n=11, 12%), cholestasis (n=10, 11%), abdominal pain (n=9, 10%), vomiting (n=7, 8%), and fever (n=5, 6%); the other 61 children were symptomless. Details of results of investigations for serology of HBeAg and anti-HBe, activity of alanine aminotransferase, and liver histology are shown in table 2. Of the symptomatic patients, 24 (83%) had hepatomegaly and three (10%) splenomegaly compared with four (6%) and none, respectively in the asymptomatic ones. In 77 children the infection was acquired by

Table 1 *Baseline clinical and serological features of children studied (n=90)*

	Serological markers				
	HbeAg+ HBV-DNA+ HBV-DNAp+	*HbeAg+ HBV-DNA+ HBV-DNAp−*	*HbeAg+ HBV-DNA− HBV-DNAp−*	*Anti-HBe+*	*Anti-HBe+ Anti-HD+*
No (%) of children	67 (74)	4 (4)	6 (7)	11 (12)	2 (2)
Male/female	44/23	2/2	2/4	6/5	1/1
Mean (SD) age (years)	6·0 (3·0)	6·1 (6·0)	6·2 (1·7)	6·4 (3·3)	4·7 (0·4)
Mean (SD) alanine aminotransferase (IU/l)	232 (289)	293 (218)	147 (148)	37 (14)	87 (40)
No (%) with symptoms	17 (25)	2 (50)	1 (17)	7 (64)	2 (100)
No (%) with hepatomegaly	21 (31)	1 (25)	1 (17)	3 (27)	2 (100)

HBV–DNAp=hepatitis B virus DNA polymerase.

Table 2 *Basal features of symptomatic and asymptomatic patients*

	Asymptomatic patients (n=61)	*Symptomatic patients (n=29)*
No (%) HBeAg positive	57 (93)	20 (69)
No (%) anti-HBe positive	4 (7)	9 (31)
Mean (SD) alanine aminotransferase (IU/l)	210 (273)	183 (254)
No (%) with diagnosis from histology of:		
Chronic active hepatitis	39 (79)	17 (59)
Chronic persistent hepatitis	8 (16)	9 (31)
Cirrhosis	1 (2)	2 (7)
Minimal changes	1 (2)	1 (3)

household contact. Two children had a previous transfusion, and in 11 children the cause of the infection was unknown.

Serology for the presence of markers for hepatitis B virus, anti-HIV, antihepatitis delta (anti-HD), and liver function tests were performed every four months using standard methods (Abbott commercial assays and SMAC Technicon). HBV–DNA was tested by dot-blot hybridisation, using a HBV–DNA probe isolated from the pBH20–HBV plasmid. The specific activity of the ^{32}P–HBV–DNA after nick-translation was 7×10^7–3×10^8 cpm/μg DNA. This technique detected less than 0·5 pg of HBV–DNA.

At the beginning of the study a liver biopsy was performed under general anaesthesia in 78 of the 90 children using a Tru-Cut needle. A second liver biopsy was performed during a mean follow up of three years (range from eight months to seven years) in 27 children. The presence of liver HDAg among anti-HD positive patients was detected by immunoperoxidase staining using a conjugated anti-HD antibody (anti-HD titre: 1/1000). Liver HBsAg and hepatitis B core antigen (HBcAg) were also tested by immunoperoxidase technique (Dakopatts a/s).

Results

In relation to the 'e' system, 77 children were HBeAg positive and 13 had anti-HBe. A total of 71 of the HBeAg positive children had circulating HBV–DNA. HBeAg positive patients had a significantly higher mean (SD) initial alanine aminotransferase activity than those with anti-HBe (232 (289) compared with 37 (14) IU/l). During follow up 24 became negative for HBeAg and HBV–DNA and 21 developed anti-HBe. The time from the beginning of the study until the seroconversion to anti-HBe varied from six months to five (2·3 (1·4)) years. The annual seroconversion rate was 14%. None of the anti-HBe children had HBV–DNA, although two were anti-HD positive.

At the end of the study all the children were clinically asymptomatic. With respect to the physical signs the frequency of hepatomegaly increased in the children who remained with HBeAg (basal 13 (24%) compared with final 31 (58%)), while a decrease was observed in children who seroconverted to anti-HBe (basal 10 (47%) compared with final three (14%)). No changes were observed in the anti-HBe children (basal five (38%) compared with final two (15%)).

Among the 21 children who seroconverted to anti-HBe, an increase of at least three times the basal alanine aminotransferase value (18 (12) times the normal value) before seroconversion was observed in 18 cases (85%). The time between the alanine aminotransferase peak and the appearance of anti-HBe was 13 (5·6) months (range: 6–28 months). These alanine aminotransferase peaks were similar to those found in acute hepatitis, although the children did not suffer any symptom or clinical complication. All the children who seroconverted to anti-HBe had normal alanine aminotransferase by

4·3 (5·8) months (range: 0–17 months) and remained so during the follow up (two years). Eight children who were anti-HBe positive initially had normal alanine aminotransferase activities. Two children returned to normal in 12 months but three remained abnormal in follow up periods of 38 to 72 months. Two of the latter had anti-HD in serum and HDAg in the liver biopsy specimen.

A basal liver biopsy was performed on 68 of the 71 children with viral replication markers (HBeAg, HBV–DNA). Although most of the children (n=54) had a chronic active hepatitis, 11 had a chronic persistent hepatitis, two had liver active cirrhosis, and one had minimal changes. After the beginning of the study, a second liver biopsy was obtained in 24 children. Of the 17 who remained positive to HBeAg, the histological picture was the same in nine cases. The other eight children showed a worsening of the histological lesion (table 3). All 17 children remained positive to liver HBsAg and HBcAg, most of them (15/17) showed a diffuse pattern of HBcAg.

Table 3 *Histological evolution of chronic hepatitis B in children*

	Liver biopsy	
	Basal	*Final*
No (%) children who remained HBeAg positive during the study (n=17):*		
Chronic active hepatitis	10 (59) (9 mild, 1 moderate)	11 (65) (7 mild, 4 moderate)
Chronic persistent hepatitis	6 (35)	3 (18)
Active cirrhosis	1 (6)	3 (18)
No (%) children who seroconverted from HBeAg to anti-HBe (n=7):†		
Chronic active hepatitis	5 (72)	—
Chronic peristent hepatitis	2 (28)	4 (57)
Minimal changes	—	3 (43)
No (%) children who remained anti-Hbe positive (n=3):‡		
Chronic active hepatitis	2 (67) (HDAg+) (1 mild, 1 moderate)	2 (67) (HDAg+) (2 moderate)
Chronic persistent hepatitis	1 (33)	—
Minimal changes	—	1 (33)

Mean (SD) time between basal and final liver biopsies: *2·7 (1·5) years; †3·8 (0·8) years; and ‡4·1 (0·6) years.

A second liver biopsy was also performed on seven children who seroconverted to anti-HBe during the three and five year periods (mean 3·8 (0·8) years). Five cases showed an improvement in the histology and in two cases the same liver lesion was observed. The basal liver biopsy specimen in these seven children was positive to HBsAg and HBcAg. In the second biopsy specimen, however, HBcAg was negative in all these cases and HBsAg remained positive. All but one had a predominantly focal pattern of HBcAg in the liver cell. The study of the HBsAg and HBcAg expression in the rest of the patients who had a liver biopsy was not available.

The basal histology of the 10 anti-HBe positive patients was two with chronic active hepatitis, six with chronic persistent hepatitis, one with inactive cirrhosis, and one with minimal changes. The liver histology from the second biopsy specimen obtained in the three anti-HBe children who remained with an abnormal alanine aminotransferase activity, resulted in the same histological findings in two cases (HDAg positive). In the HDAg negative patient, an amelioration of the histological lesion was observed.

Discussion

In our experience children with hepatitis B virus replication markers suffered a more active liver disease biochemically and histologically than those without replication. These results are in accordance with previous reports.[7 8] Although at the end of the study all the children were asymptomatic, in those who seroconverted to anti-HBe a decrease in the frequency of hepatomegaly was observed, with an important histological improvement. In contrast, children who remained HBeAg positive had an increase in the frequency of hepatomegaly and a progression of the histological lesion (in some cases to liver active cirrhosis). This result is lower than those reported by other authors,[4 5] and different from that of Bortolotti *et al* who did not find progression to cirrhosis.[2 7] A possible explanation could be the technical differences in the performance of the liver biopsies. Dupuy *et al* obtained the biopsy specimens under laparoscope control,[4] which could increase the probability of a diagnosis of cirrhosis.[8] We used a blind biopsy technique with a Tru-Cut rather than a Menghini needle, as was used by Bortolotti *et al.*[7] Therefore, laparoscope and the longer cylinder obtained with our needle will most likely account for the differences.

Additionally, our data differ from that of Lai *et* *al.*[9] Our children with hepatitis B virus replication markers had an abnormal alanine aminotransferase activity, while most of their Chinese children had normal activities. This variation could be explained by racial and epidemiological differences. Chinese children acquired the infection at birth, while ours did not. The interferon concentrations in lymphocytes of Chinese people are normal but are abnormal in white races.[10]

All the children from our study who seroconverted remained HBsAg positive; this is in accordance with previous studies.[6 8] Thus the risk of the development of hepatoma probably persists in these children.[11] Further studies are required to indicate if HBV–DNA remains in an integrated form after seroconversion.

The children with persistent viral replication had a diffuse pattern of HBcAg in the liver. In contrast, those children who seroconverted to anti-HBe showed a focal pattern. These results agree with those of Bortolotti *et al,*[12] and so testing for HBcAg in the liver could be useful as a prognosis indicator.

During seroconversion, an increase in alanine aminotransferase activity similar to that in acute hepatitis was observed in most of the children. In our experience, however, only 50% of the adults who seroconverted had a previous alanine aminotransferase increase.[13] Although we are unsure as to the reason for this difference between adults and children from the same population, a possible explanation is the difference in their immune systems. In support of this theory, we observed an important regression of liver disease in adults during seroconversion while none was detected in the children.[14] This variation could be due to the fact that liver cirrhosis is less common in children, or also that they regenerate the liver cells more quickly than adults.

With the exception of two patients with delta superinfection, all the children with anti-HBe and abnormal alanine aminotransferase activity at the beginning of the study had normal alanine aminotransferase at the end of the follow up period. Therefore, the anti-HBe status in children correlated with a normal alanine aminotransferase activity and good prognosis in the absence of the delta virus. During the follow up reactivation of viral replication in the anti-HBe children did not take place as all the children remained HBV–DNA negative in contrast with that reported in adults.[15] A similar lack of HBV–DNA among anti-HBe children has been reported.[2 5] This suggests that clearance of all HBV–DNA replicative forms in hepatocytes occurred in these children. In adults, however, HBV–DNA supercoiled could remain in hepatocytes due to the lack of elimination and consequently reactivation takes place in about 40% of anti-HBe cases (unpublished data).

This study confirms the high frequency of advanced liver disease in association with chronic hepatitis B virus infection and a persistently raised serum transaminase activity for a period of more than six months. Such patients should be considered for treatment with antiviral agents both to limit progression of liver disease and to reduce the risks of HBV–DNA integration and the subsequent development of hepatoma.[16 17] In such a case, if the treatment is efficient, the prognosis of the disease will be more favourable.[18]

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References

[1] Nordentfelt E, Kjellen L. Dane particles, DNA polymerase and e antigen in two distinct categories of hepatitis B antigen carriers. *Intervirology* 1975;**5**:225–32.

[2] Bortolotti F, Cadrobbi P, Rugge M, Pontisso P, Armigliato M, Realdi G. Evolution of chronic hepatitis B of children towards a 'healthy' HBsAg carrier state: results a prospective study. *J Hepatol* 1986;**3**:S35.

[3] Bortolotti F, Cadrobbi P, Crivellaro C, Bertaggia A, Alberti A, Realdi G. Chronic hepatitis type B in childhood: longitudinal study of 35 cases. *Gut* 1981;**22**:499–504.

[4] Dupuy JM, Kostewitz E, Alagille D. Hepatitis B in children. *J Pediatr* 1978;**98**:17–20.

[5] Codoñer P, Scotto J, Hadchouel M, Bernard O, Alagille D. Evolution des hepatites chroniques liées au virus B chez l'enfant. Etude de l'ADN viral sérique. *Gastroenterol Clin Biol* 1985;**9**:516–21.

[6] Bortolotti F, Cadrobbi P, Crivellaro C, *et al.* Changes in hepatitis Be antigen/antibody system in children with chronic hepatitis B virus infection. *J Pediatr* 1983;**103**:718–22.

[7] Bortolotti F, Calzia R, Cadrobbi P, *et al.* Liver cirrhosis associated with chronic hepatitis B virus infection in childhood. *J Pediatr* 1986;**108**:224–7.

[8] Codoñer P, Brines J, Bernard O, Hadchouel M, Alagille D, Scotto J. ADN serico del virus B de la hepatitis en niños con infeccion crónica. *An Esp Pediatr* 1986;**26**:98–104.

[9] Lai CL, Lin HJ, Yeoh EK, Lok AS, Wu PC, Yeung CY. Placebo-controlled trial of recombinant α_2-interferon in chinese HBsAg carrier children. *Lancet* 1987;**ii**:877–80.

[10] Kato Y, Nakagawa H, Kobayashi K, Hattori N, Hatano K. Interferon production by peripheral lymphocytes in HBsAg positive liver disease. *Hepatology* 1982;**2**:789–90.

[11] Kew MC. The possible etiologic role of hepatitis B virus in hepatocellular carcinoma: evidence from Southern Africa. In: Chisari, ed. *Advances in hepatitis research.* New York: Masson, 1984:203–15.

[12] Bortolotti F, Alberti A, Cadrobbi P, Rugge M, Armigliato M, Realdi G. Prognostic value of hepatitis B core antigen (HBcAg) expression in the liver of children with chronic hepatitis type B. *Liver* 1985;**5**:40–7.

[13] Porres JC, Carreño V, Mora I, *et al.* Different doses of recombinant interferon alpha in the treatment of chronic hepatitis B patients without antibodies against the human immunodeficiency virus. *Hepatogastroenterology* 1988;**35**: 300–3.

[14] Carreño V, Porres JC, Mora I, *et al.* Prolonged (6 months) treatment of chronic hepatitis B virus infection with recombinant leukocyte A interferon. *Liver* 1987;**7**:325–32.

[15] Perrillo RP, Campbell CR, Sanders GE, Regenstein FG, Bodicky CJ. Spontaneous clearance and reactivation of hepatitis

B virus infection among homosexuals with chronic type B hepatitis. *Ann Intern Med* 1984;**100**:43–6.

[16] Perrillo RP. Anti-viral therapy of chronic viral hepatitis. *Current Opinion in Gastroenterology* 1988;**4**:420–7.

[17] Perrillo RP, Regenstein FG, Peters NG, *et al.* Prednisolone withdrawal followed by recombinant alpha interferon. Treatment of chronic hepatitis B. A randomised control trial. *Ann Intern Med* 1988;**109**:95–100.

[18] la Banda F, Ruiz M, Carreño V, *et al.* Recombinant α_2-interferon treatment in children with chronic hepatitis B. *Lancet* 1988;**i**:250.

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Precocious puberty in girls: early diagnosis of a slowly progressing variant

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SUMMARY An attempt was made to identify the less severe cases of precocious puberty and to describe their natural course. A group of 17 girls with precocious puberty and a bone age advance over chronological age of less than two years (group 1) was compared with a group of 19 patients with severe precocious puberty and bone age advance of two years or more (group 2). Mean (SEM) plasma oestradiol concentrations were 82 (30) pmol/l and 164 (21) pmol/l ($p<0{\cdot}05$), vaginal maturation indexes were 16 (5) and 41 (4), and plasma somatomedin C concentrations were 1·0 (0·2) U/ml (n=8) and 2·1 (0·3) U/ml (n=16) in groups 1 and 2, respectively. The time between onset and diagnosis of secondary sexual characteristics was about one year in both groups. After two years' follow up the untreated patients in group 1 had maintained their predicted final height. These changes were in contrast to those observed at first examination in patients in group 2 who had a mean (SD) predicted final height of −1·3 (0·2) and a mean bone age advance of 3·0 (0·2) years. These data show that bone age advance to chronological age, and plasma somatomedin C concentrations measured at initial evaluation are helpful in identifying less severe and potentially slow progressing forms of central precocious puberty.

Children with central precocious puberty have a premature increase in the secretion of sex hormones that leads to acceleration of their growth rate. At the same time excessive progression of bone age may lead to short adult stature. The course of sexual precocity is variable, however, and in some cases normal growth continues with no reduction in predicted final height.[1] This clinical heterogeneity may partly explain the difficulty that has been encountered in establishing the effectiveness of treatment with cyproterone acetate[2] or medroxyprogesterone.[3] More recently drugs such as luteinising hormone releasing hormone analogues have been shown to suppress gonadotrophin secretion and gonadal activity completely. Data from short term trials have already shown that there is an increase in the predicted final height.[4–8] We have studied the spontaneous course of precocious puberty according to its initial presentation, to evaluate the early use of luteinising hormone releasing hormone analogues.

Patients and methods

Thirty six girls with idiopathic precocious puberty who had been regularly followed up in the paediatric endocrinology unit were assigned to this study. Informed consent was obtained from both them and their parents. The diagnostic criterion of precocious puberty was the occurrence of oestrogenic activity in association with the appearance of pubic hair before age of 8 years. Primary ovarian follicular cysts and adrenal diseases were ruled out. The plasma concentrations of β human chorionic gonadotrophin and α fetoprotein were normal. A computed tomogram of the head was carried out in all cases and was normal. No patient had previously received treatment for precocious puberty. Growth hormone secretion, evaluated by the arginine-insulin tolerance test, was normal.

Patients were arbitrarily classified into two groups (table 1) according to their bone age advance over chronological age at first examination: group 1 comprised patients in whom the advance was less than two years (cases 1–17) and group 2, patients in whom it was more than two years (cases 18–36). The bone age advance was selected as a discriminatory criterion because it had been used in this group to decide which patients were to receive treatment with the luteinising hormone releasing hormone

Table 1 *Clinical and biological data for 36 girls with precocious puberty at time of first examination*

Case No	*Chronological age (years)*	*Bone age (years)*	*Height (SD)*	*Pubertal stage*[9]	*Plasma oestradiol concentration (pmol/l)*	*Vaginal maturation index*	*Peak plasma luteinising hormone concentration (IU/l)*	*Peak follicle stimulating hormone concentration (IU/l)*	*Plasma somatomedin C/ insulin like growth factor I concentration (U/ml)*
Group 1	Bone age less than two years in advance of chronological age								
1	2	2·7	2	B3 P1M	0	40	4·3	14	0·8
2	5·1	6·5	3·5	B2 P2	37	0	8	1·6	0·8
3	5·6	6·5	1	B1 P1M	132	17	1·7	1·5	Not measured
4	5·6	6·1	1	B1 P1M	18	41	1	0·5	1·7
5	6	6	−1·7	B2 P2	77	0	3	2·5	0·3
6	6·1	7	2	B2 P2	320	50	3	2·5	Not measured
7	6·2	7·8	4	B2 P2	0	20	5	7	Not measured
8	6·8	7·8	3	B2 P2	37	25	2·4	10	1·3
9	6·8	7	0	B2 P2	18	0	4	6	1·3
10	7	7·5	2·5	B2 P2	37	Not measured	7·1	7·1	1
11	7·1	7·8	1	B2 P2	18	Not measured	1·4	5·5	Not measured
12	7·5	8·8	1·5	B2 P2	37	0	2·4	8	0·6
13	7·7	8·8	1·3	B2 P2	0	0	Not measured	Not measured	Not measured
14	7·7	8·8	1	B2 P2	88	Not measured	2·3	2·4	Not measured
15	7·7	7·8	2	B2 P2	455	Not measured	25	5	Not measured
16	7·8	7·8	2	B2 P2	0	Not measured	2·6	8·3	Not measured
17	8	7·8	1	B2 P2	117	0	3·3	10	Not measured
Mean (SEM)	6·5 (0·4)	7·2 (0·4)	1·6 (0·3)		82 (30)	16 (5)	4·8 (1·4)	5·8 (0·9)	1·0 (0·2)
Group 2	Bone age more than two years in advance of chronological age								
18	3·4	5·5	3	B2 P3M	183	50	28	14	1·3
19	3·5	6	3	B3 P2	132	45	—	—	1·9
20	4·6	10·5	4·5	B2 P2	55	40	35	20	1·7
21	6·2	9	2·0	B3 P2	183	55	10	10	4·7
22	6·6	10·5	3·5	B4 P2	37	42	30	12·5	2·3
23	7·2	10·5	2	B3 P4	110	49	8	9	—
24	7·7	10	1	B2 P4	147	3	3	7·3	1·3
25	7·7	10·5	1·5	B3 P3	257	50	10	7	3
26	7·7	11	1·5	B3 P3	73	21	12	11	—
27	7·8	10·5	2	B2 P2	73	45	11	13	1·2
28	8	10·5	3	B3 P3	128	0	8·5	1	0·8
29	8·2	11	3·0	B3 P3	202	43	10	6·5	1·2
30	8·3	11	2·5	B4 P4	271	40	3	6·3	2·7
31	8·4	12	2·5	B3 P2M	238	58	66	12	1·9
32	8·8	12	−0·5	B2 P2	220	52	10	9·3	2·9
33	8·8	11	2	B3 P3	110	40	8	7·6	0·9
34	8·8	12	3·5	B3 P2M	183	52	11	5	3·3
35	8·8	11	2·5	B3 P3	110	47	16	7	2·5
36	8·9	12·5	2	B4 P5M	404	50	44	31	—
Mean (SEM)	7·3 (0·4)	10·4 (0·4)	2·4 (0·2)		164 (21)	41 (4)	18 (4)	10·5 (1·5)	2·1 (0·3)
p Value compared with group 1	<0·2	<0·001	<0·1		<0·05	<0·01	<0·01	<0·01	<0·01

analogue. In group 1 the spontaneous course of precocious puberty was followed up for a period of two years after the first examination and the patients received no treatment, with the consent of their parents. The patients in group 2 were treated with the analogue (Buserelin) after the first examination.

The mean (SEM) chronological ages in the two groups at the time of first examination was 6·5 (0·4) years (range 2–8) and 7·3 (0·4) years (range 3·4–8·9), respectively.

The mean (SEM) time intervals between the onset of sexual development and the first examination were similar in both groups, being 0·7 (0·2) years (range 0·2–1) and 1·0 (0·2) (range 0·3–1·1), respectively.

Puberty ratings were made according to Tanner's scale.[9] Height changes were expressed as standard deviation scores taking the chronological age or the bone age as the reference measurement. Final heights were predicted according to the method Bayley and Pinneau[10] using the bone age as assessed by Greulich and Pyle.[11] Final predicted heights were expressed in relation to the mean normal adult height using standard deviation scores.[12]

All patients were evaluated according to previously published methods for growth hormone secretion (arginine-insulin tolerance test[13]) and basal serum values of oestradiol and somatomedin C/insulin like growth factor I.[14] The gonadal hypothalamic-pituitary axis was investigated by basal and luteinising hormone releasing hormone stimulated measurements of plasma luteinising hormone, and follicle stimulating hormone, as previously reported.[15] The vaginal maturation index was evaluated by vaginal smear examination with an upper normal prepubertal value of 35.[16]

The vaginal maturation index was not evaluated in cases 10, 11, 14, 15, and 16 at the time of their first examination. Cases 13 and 19 were not tested for luteinising hormone releasing hormone at their initial examination. All data are expressed as mean (SEM) and statistical comparisons were made by Student's paired *t* test on the same group, and by the unpaired *t* test between groups 1 and 2.

Results

COMPARISON AT TIME OF DIAGNOSIS BETWEEN THE TWO GROUPS OF PATIENTS

Tables 1 and 2 show the clinical presentation and biological data of the two groups. The distribution of the breast development stage in relation to the bone age advance is shown in the figure. The mean chronological ages at the first evaluation and the mean time from the onset of sexual development were similar in both groups. By definition the mean bone age advance (expressed as bone age minus chronological age) was significantly lower in patients in group 1 (0·7 (0·1) years) compared with group 2 (3 (0·2) years) (p<0·001). The mean height gains during the year before the initial evaluation were similar in both groups, 7·8 (0·8) cm and 8·5 (0·4) cm, respectively. Patients of group 1 were, however, slightly but not significantly shorter, with a mean (SD) height score for chronological age of 1·6 (0·3) above the normal mean compared with 2·4 (0·2) for patients of group 2 (p<0·05).

Patients in group 1 also had fewer clinical signs of excessive oestrogen production when first seen: vaginal bleeding in two cases (cases 3 and 4), breast development at Tanner's stage 2 in 14 patients, and stage 3 in one case (table 1). Pubic hair was present

Table 2 *Spontaneous growth and bone maturation during the two years following the first examination in girls with precocious puberty and moderate oestrogen activity (group 1)*

Case No	*Bone age −chronological age (years)*		*Height (SD)*		*Height prediction (standard deviation score)*	
	0	*After 2 years*	*0*	*After 2 years*	*0*	*After 2 years*
1	0·7	0·9	2·0	2·0	Not known	Not known
2	1·4	0·9	3·5	3	Not known	1
3	0·9	0·9	1·0	2	Not known	0·8
4	0·5	1·6	1·0	2	Not known	0
5	0	1·6	−1·7	−0·3	Not known	−2·2
6	0·9	1·2	2·0	1·6	0·1	0
7	1·6	0·5	4·0	3	1·2	1·5
8	1·0	0·8	3·0	3	−0·1	1·4
9	0·2	0·9	0·0	−0·5	−1·1	−0·9
10	0·5	0·9	2·5	2·5	1·8	1·1
11	0·7	1·5	1·0	1	0·5	−0·3
12	1·3	1·1	1·5	0·7	0	−1·2
13	1·1	0·9	1·3	2·5	−0·5	0
14	1·1	1·2	1·0	0	0·2	Not known
15	0·1	1·8	2·0	3	1·2	−0·1
16	0	1·5	2·0	2	1·5	1
17	−0·2	1·1	1·0	0·8	0·5	−0·1
Mean (SEM)	0·7 (0·1)	1·1 (0·1)*	1·6 (0·3)	1·6 (0·4)	0·4 (0·2)	0·1 (0·3)

*p<0·05 compared with value at time 0.

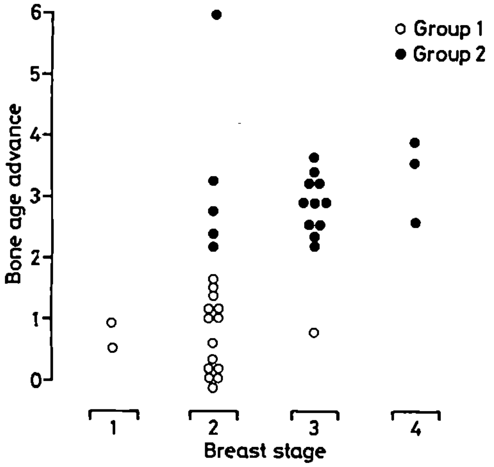

Figure *Distribution of the breast development stage in relation to bone age advance (bone age–chronological age) in girls with precocious puberty.*

at first examination in 14 patients (stage 2), and the remaining three patients (cases 1, 3, and 4) developed pubic hair within eight months of diagnosis. All patients had pubic hair before the age of 8 years. Patients 7, 9, 11, and 16 had recurrent and spontaneously reversible spurts of breast development.

The initial biological data are shown in table 1. In group 1, the mean concentration of circulating oestradiol was 82 (30) pmol/l (range 0–455). All except cases 6 and 15 had concentrations of less than 132 pmol/l. The mean vaginal maturation index was 16 (5) (range 0–50), mean luteinising hormone peak was 4·8 (1·4) IU/l (range 1–25), and the mean follicle stimulating hormone peak was 5·8 (0·9) IU/l (range 0·5–14). Eleven of 17 girls had no biochemical or cytological signs of oestrogen impregnation (oestradiol concentration <92 pmol/l and vaginal maturation index <35). In spite of the persistence of breast development, the two patients with the highest initial plasma oestradiol concentrations (cases 6 and 15) had prepubertal oestradiol concentrations and vaginal maturation indexes when re-evaluated six months later. Pelvic ultrasound examination did not disclose any ovarian cysts.

In contrast, most patients in group 2, whose bone age advance was at least two years, had overt clinical and biological signs of excessive oestrogen production when first seen. Their breast development was equal or above stage 3 in 14 cases. In the remaining four cases it was stage 2. In this group, the mean plasma concentration of oestradiol was 164 (21) pmol/l (range 37–404), the mean vaginal maturation index was 41 (4) (range 0–58), the mean peak luteinising hormone was 18 (4) IU/l (range 3–66), and the mean peak follicle stimulating hormone was 10·5 (1·5) IU/l (range 1–31). All the values in group 2 were significantly greater than the mean values in group 1 (table 1). They were thought to reflect a more mature hypothalamic gonadotrophin axis.

Plasma somatomedin C concentrations were measured in only eight patients from group 1 and 16 patients from group 2 (table 3). The mean plasma somatomedin C concentration of 1·0 (0·2) U/ml (range 0·3–1·7) in group 1 was significantly lower than that of 2·1 (0·3) U/ml (range 0·8–4·7) in group 2 (p<0·01). These two groups of patients also differed significantly in their plasma oestradiol concentrations (33 (11) pmol/l in group 1 and 154 (18) pmol/l in group 2, p<0·001). The growth rate was similar in the two groups, however, (7·8 (0·8) and 8·9 (0·4) cm in groups 1 and 2, respectively). We found no correlation between plasma oestradiol concentration and growth rate or plasma somatomedin C concentrations, either within the groups or in the whole population.

GROWTH IN UNTREATED PATIENTS WITH CENTRAL PRECOCIOUS PUBERTY AND LOW OESTROGEN ACTIVITY

The spontaneous growth and bone maturation in patients in group 1 were analysed after a two year follow up period to evaluate the effect of persistently low oestrogenic activity (table 2). After two

Table 3 *Plasma somatomedin C/insulin like growth factor I concentrations and growth in girls with mild (group 1) or severe (group 2) precocious puberty at time of first examination. Values are expressed as mean (SEM)*

Group	*No of subjects*	*Chronological age (years)*	*Bone age (years)*	*Bone age–chronological age (years)*	*Plasma somatomedin C/ insulin like growth factor I concentration (U/ml)*	*Plasma oestradiol concentration (pmol/l)*	*Height gain (cm/year)*
1	8	6·0 (0·6)	6·6 (0·7)	0·7 (0·2)	1·0 (0·2)	9 (3)	7·8 (0·8)
2	16	7·2 (0·5)	10·2 (0·5)	3·0 (0·3)	2·1 (0·3)	42 (5)	8·9 (0·4)
p Value		<0·1	<0·001	<0·001	<0·01	<0·001	<0·3

years the mean advance of bone age over chronological age was 1·1 (0·1) years (range 0·5–1·8). This was slightly but significantly higher than the value of 0·7 (0·1) years found at the time of diagnosis ($p<0·05$). The bone age advance had progressed by more than one year in only four of 17 children (cases 4, 5, 15, and 16). It had remained unchanged or decreased in six cases and progressed slightly in the seven others. Height for chronological age, expressed by the standard deviation score, had a mean (SD) value of 1·6 (0·4) compared with a similar initial value of 1·6 (0·3). The mean (SD) final height prediction in these patients remained unchanged (0·1 (0·3)) from the initial value in the group of 12 patients evaluated at the time of diagnosis (0·4 (2·2)). Interestingly, among the four patients with the greatest progression of bone maturation, only one (case 5) had a low final height at 2·2 standard deviations below the normal mean.

The results for the patients in group 1 were also compared with the initial data for patients in group 2 at the time of diagnosis when precocious puberty had already accelerated bone maturation by more than two years. The mean (SD) predicted final height of patients in group 2 was −1·3 (0·2) below the normal mean, a value significantly lower than that calculated for patients in group 1 (0·1 (0·3)) after a much longer period of spontaneous progression of the disease ($p<0·01$). This comparison indicates that, despite nearly three years exposure to low or variable oestrogen activity in group 1, growth had remained sufficient in relation to bone maturation to permit a satisfactory mean final height prediction. This had not been the case in patients in group 2 seen after an average period of only one year who presented with pronounced oestrogen activity and rapidly progressing bone maturation.

Discussion

The results of this study showed that mild forms of central precocious puberty in girls can be identified at the first examination. They seem to be characterised by a combination of low plasma oestradiol and somatomedin C, and normal or slightly advanced bone age at the time of diagnosis. We have shown that the course of the disease in these cases is also different from the usually severe forms of precocious puberty.

Bone maturation and height gain do not progress in parallel when sex hormones are secreted before puberty, and it is known that precocious puberty may accelerate epiphyseal fusion and lead to a reduction in final height. The fact that some patients in this group initially presented with normal or close to normal bone age provided an opportunity to assess the effect of moderate oestrogen activity on growth and to discuss the need for treatment with luteinising hormone releasing hormone analogue. The group of girls with mild precocious puberty seen nine months after the onset of clinical evidence of ovarian activity had only a moderate advance in bone age. The predicted final height remained normal. This indicates that height gain had been appropriate for bone age progression during this early period of the disease. This effect on skeletal growth was probably caused by low circulating oestradiol concentrations during the preceding year. It is comparable with the changes observed during the early period of normal puberty when growth acceleration accompanies or even precedes the appearance of sexual characteristics.[17] Plasma somatomedin C values increase during normal puberty, and it has been suggested that this phenomenon in girls is mediated by the oestrogens indirectly through increased secretion of growth hormone rather than through a direct effect of oestradiol.[18 19]

In the present report, the plasma somatomedin C values were in the prepubertal range or slightly raised in girls with mild forms of precocious puberty, and pubertal in those with the severe form. A more complete evaluation of growth hormone secretion using spontaneous growth hormone profiles could not be performed in these patients, but in view of their plasma somatomedin C values it is possible that the growth hormone secretion in the mild form of precocious puberty did not increase to the extent seen in normal puberty during the Tanner P3 stage[20–22] or in patients with severe precocious puberty.[18 19 23–25] One might consider, therefore, that in addition to bone age the circulating value of plasma somatomedin C at the first examination reflected the ovarian activity, hence the severity of the disease. It is tempting to relate these data to recently reported results of skeletal response to low doses of oestrogens in girls with Turner's syndrome.[26 27] These authors reported a significant acceleration of growth without a concomitant change in plasma somatomedin C. When low doses of ethinyloestradiol were used in these patients, growth rates increased without changes in bone maturation or plasma somatomedin C concentration. In the present study, a similar course of events occurred in the group of girls with less severe precocious puberty. In contrast, when pronounced oestrogen activity was present at first examination, its effect was predominant on bone maturation, leading to a reduced final height prediction. This was because the growth rate was not appropriate for bone age progression, in contrast to the group with moderate precocious puberty.

The spontaneous course of idiopathic precocious puberty in girls varies in presentation of symptoms and rate of progression: some cases show accelerated development while others may progress slowly or have totally regressive characteristics.[1] The results of this study show that the lack of excessive progression of bone age and the plasma prepubertal somatomedin C values nine to 12 months after the onset of puberty are good indicators of moderate oestrogen activity. It is of interest that most of these cases of mild precocious puberty at time of diagnosis did not develop into severe and rapidly progressing precocious puberty. Furthermore, the age distribution did not differ between the groups. We suggest that girls with such moderate forms of precocious puberty be followed up for at least one year before deciding whether or not to have treatment with luteinising hormone releasing hormone analogue. Such treatment may be delayed as long as the final height prediction can be closely followed. Regression of pubertal signs may occur. If treatment is decided upon, it may be appropriate to re-evaluate the hypophyseal ovarian activity after two years of follow up to avoid unduly prolonged treatment. Probably all of these factors should be taken into consideration before committing a girl with central precocious puberty to treatment with the analogue.

In conclusion, an untreated group of girls with idiopathic central precocious puberty and moderate ovarian activity was followed for a period of two years. The data obtained at their first examination and in the course of their disease showed that bone maturation and plasma somatomedin C values are helpful in identifying the less severe and potentially slowly progressing forms of central precocious puberty. These cases might not require immediate treatment with the luteinising hormone releasing hormone analogue and a close follow up may be preferred before treatment to evaluate their natural course.

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References

[1] Brauner R, Thibaud E, Rappaport R. Pubertés précoces centrales spontanément régressives chez la fille. Incidence sur les indications thérapeutiques dans les pubertés précoces. *Ann Pediatr* 1987;**34**:70–4.

[2] Werder EA, Murset G, Zachmann M, Brook C, Prader A. Treatment of precocious puberty with cyproterone acetate. *Pediatr Res* 1974;**8**:248–56.

[3] Kaplan SA, Ling SM, Irani NG. Idiopathic isosexual precocity. Therapy with medroxyprogesterone. *Am J Dis Child* 1968;**116**: 591–8.

[4] Styne DM, Harris DA, Egli CA, *et al.* Treatment of true precocious puberty with a potent luteinizing hormone-releasing factor agonist: effect on growth, sexual maturation, pelvic sonography, and the hypothalamic-pituitary-gonadal axis. *J Clin Endocrinol Metab* 1985;**61**:142–51.

[5] Pescovitz OH, Comite F, Hench K, *et al.* The NIH experience with precocious puberty: diagnostic subgroups and response to short-term luteinizing hormone releasing hormone analogue therapy. *J Pediatr* 1986;**108**:47–54.

[6] Beopple PA, Mansfield MJ, Wiermann ME, *et al.* Use of a potent, long acting agonist of gonadotropin-releasing hormone in the treatment of precocious puberty. *Endocr Rev* 1986;**7**: 24–33.

[7] Brauner R, Rappaport R. Traitement des pubertés précoces centrales par un analogue du LHRH (HOE 766, Buserelin). Effet sur la croissance et la maturation osseuse après deux années de traitement. *Arch Fr Pediatr* 1987;**44**:271–6.

[8] Brauner R, Thibaud E, Bishop P, Sizonenko PC, Rappaport R. Long term results of GnRH analogue (Buserelin) treatment in girls with central precocious puberty. *Acta Paediatr Scand* 1985; **74**:945–9.

[9] Tanner JM. *Growth at adolescence.* Oxford: Blackwell, 1978: 28–39.

[10] Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with Greulich Pyle hand standards. *J Pediatr* 1952;**50**:432–41.

[11] Greulich WW, Pyle SI. *Radiographic atlas of skeletal development of the hand and wrist.* 2nd ed. Stanford: University Press, 1959.

[12] Sempe M, Pedron G, Roy-Pernot MP. *Auxologie, méthode et séquences.* Paris: Theraplix, 1979.

[13] Penny R, Blizzard RM, Davis MT. Sequential arginine and insulin tolerance test on the same day. *J Clin Endocrinol Metab* 1969;**29**:1499–501.

[14] Furlanetto RW, Underwood LE, Van Wyk JJ, D'Ercole AJ. Estimation of Somatomedin-C levels in normals and patients with pituitary disease by radioimmunoassay. *J Clin Invest* 1977;**60**:648–57.

[15] Rappaport R, Brauner R, Czernichow, P, *et al.* Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors. *J Clin Endocrinol Metab* 1982; **54**:1164–8.

[16] Meisels A. Computed cytohormonal findings in 3307 healthy women. *Acta Cytol* 1965;**9**:328–33.

[17] Tanner JM, Whitehouse RH, Hughes PC, Carter BS. Relative importance of growth hormone and sex steroids for the growth at puberty of trunk length, limbs length, and muscle width in growth hormone deficient children. *J Pediatr* 1976;**89**:1000–8.

[18] Harris DA, Van Vliet G, Egli CA, *et al.* Somatomedin-C in normal puberty and in true precocious puberty before and after treatment with a potent luteinizing hormone-releasing hormone agonist. *J Clin Endocrinol Metab* 1985;**61**:152–9.

[19] Ross JL, Pescovitz OH, Barnes K, Loriaux DL, Cutler GB. Growth hormone secretory dynamics in children with precocious puberty. *J Pediatr* 1987;**110**:369–72.

[20] Finkelstein JW, Roffwarg HP, Boyar RM, Kream J, Hellman L. Age related change in the twenty-four-hour spontaneous secretion of growth hormone. *J Clin Endocrinol Metab* 1972;**35**: 665–70.

[21] Zadik Z, Chalew SA, Mc Carter RJ, Meistas M, Kowarski AA. The influence of age on the twenty-four-hour integrated concentration of growth hormone in normal individuals. *J Clin Endocrinol Metab* 1985;**60**:513–6.

[22] Miller JD, Tannebaum GS, Colle E, Guyda HJ. Daytime pulsatile growth hormone seretion during childhood and adolescence. *J Clin Endocrinol Metab* 1982;**55**:989–94.

[23] Pescovitz OH, Rosenfeld RG, Hintz RL, *et al.* Somatomedin-C in accelerated growth in children with precocious puberty. *J Pediatr* 1985;**107**:20–5.

[24] Rappaport R, Prevot C, Brauner R. Somatomedin C and growth in children with precocious puberty: A study of the effect of the level of GH secretion. *J Clin Endocrinol Metab* 1987;**65**: 1112–17.

[25] Mansfield MJ, Rudlin CR, Crigler JF, *et al.* Changes in growth and serum growth hormone and plasma somatomedin-C levels during suppression of gonadal sex steroid secretion in girls with central precocious puberty. *J Clin Endocrinol Metab* 1988; **66**:3–9.
[26] Ross JL, Cassorla FG, Skerda M, Valk IM, Loriaux DL, Cutler GB. A preliminary study of the effect of estrogen dose on growth in Turner's syndrome. *N Engl J Med* 1983;**309**:1104–6.
[27] Ross JL, Long LM, Skerda M, *et al.* Effect of low doses of estradiol on 6 month growth rates and predicted height in patients with Turner syndrome. *J Pediatr* 1986;**109**:950–3.

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Transient infantile hyperthyrotrophinaemia

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SUMMARY Sixteen cases of transient infantile hyperthyrotrophinaemia were followed up for two to seven years. Concentrations of serum triiodothyronine, thyroxine, and free thyroxine were maintained within the normal range in all cases. All but one child, who had a hearing disturbance, showed normal mental development with normal physical and skeletal maturation. Eleven children had normal concentrations of serum thyroid stimulating hormone and no signs or symptoms of thyroid dysfunction; in three children, diffuse small goitres developed and two further children showed relapse with slightly raised concentrations of thyroid stimulating hormone.

It is concluded that 'transient infantile hyperthyrotrophinaemia' is a syndrome, which differs from typical transient neonatal hypothyroidism, and that careful follow up is necessary because some children show signs of mild pituitary-thyroid dysfunction in later childhood.

Transient infantile hyperthyrotrophinaemia was first reported by Miyai *et al* in 1979.[1] Since then many similar cases have been reported[2 3] with a total of 98 cases in Japan by 1986.[4]

Differentiation of transient infantile hyperthyrotrophinaemia from mild congenital hypothyroidism or transient neonatal hypothyroidism is difficult unless suspected cases are carefully followed up. No long term studies have been made on this syndrome, however, so confirmatory diagnosis has not been possible and the prognosis for physical and psychomotor development is uncertain.

In this paper we report follow up studies on 16 children with transient infantile hyperthyrotrophinaemia.

Patients and methods

During eight years from November 1975 to November 1983, 281 468 infants born in the Osaka area were screened by measuring thyroid stimulating hormone in filter paper blood samples, and 257 neonates were recalled according to the programme reported previously.[5] There were 84 infants with a high concentration of thyroid stimulating hormone (>17 mU/l), and of these 16 infants (10 boys and six girls) were diagnosed as having transient infantile hyperthyrotrophinaemia by the criteria shown in table 1. All were delivered normally at full term and had normal birth weights and lengths. None had clinical features of congenital hypothyroidism[6] and bone age was normal in the infants where radiography was performed. None had a maternal history of excessive or low iodine intake or of amniofetography.

Maternal antithyroglobulin haemagglutination antibodies (TGHA) and antithyroid microsome haemagglutination antibody (MCHA) were negative as was thyroid stimulating hormone binding inhibitor immunoglobulin (TBII) in the cases examined.

These 16 infants were followed up from two to

Table 1 *Criteria for the diagnosis of transient infantile hyperthyrotrophinaemia*

1 Serum thyroid stimulating hormone concentration (2–8 weeks of age) >4 SD above mean for normal controls (mean (SD) 7·4 (2·3) mU/l; mean+4 SD 17 mU/l)
2 No contamination with heterophilic antibodies (linear relationship in dilution experiment)
3 Serum thyroid stimulating hormone concentration (2–9 months of age) decreases to normal and remains normal until 1 year of age
4 Serum thyroxine, triiodothyronine, and free thyroxine concentrations are maintained within the normal range
5 No goitre or sublingual mass due to an ectopic thyroid (normal thyroid radioiodine uptake and scintigram)
6 No signs or symptoms of congenital hypothyroidism and normal bone maturation
7 No maternal history of thyroid disorder, intake of antithyroid agents, or excessive or deficient iodide intake

seven years with reference to growth and clinical progress. Mental development was assessed by the Tsumori-Inage or Tsumori-Isobe developmental scales, which are usually used in Japan to evaluate psychomotor development of infants and children.[7] In some cases the IQ was assessed by the Wechsler intelligence scales for children.[8]

Hormones were measured by radioimmunoassay using commercial kits: thyroid stimulating hormone (Daiichi Radioisotope Laboratory), thyroxine and triiodothyronine (Eiken Immunochemical Laboratory), and free thyroxine (Gamma Coat RIA kit, Clinical Assays Inc or Amerlex Free T_4 RIA Kit, Amersham Radiochemical Centre).

TGHA and MCHA were measured by a commercial kit (Fujizoki Co); the basal metabolic rate was measured with an open circuit indirect calorimeter.[9]

Statistical analyses were performed by the two sample Student's *t* test.

Results

The initial thyroid function test results are shown in table 2. None of the infants had appreciable clinical features of cretinism on the score of Smith *et al*,[6] and in the infants studied for bone age none had abnormal bone maturation. Concentrations of serum thyroxine, triiodothyronine, and free thyroxine were all normal as were the basal metabolic rates of those infants examined. Thyroid uptake of ^{123}I was also within the normal range, and scintigrams showed a normal shape, size, and location of the thyroid.

Changes in the concentrations of serum thyroid stimulating hormone, thyroxine, and triiodothyronine during follow up for two to seven years are shown in fig 1. Five infants (cases 5, 6, 12, 13, and 15) were given L-thyroxine for two to six months after birth; the other infants received no medication.

According to outcome we have tentatively classified the 16 infants into three groups (table 3). Group A had normal thyroid function (cases 1–11; fig 1A) and concentrations of serum thyroxine, triiodothyronine, and free thyroxine were within the normal range of age matched controls. Group B had relapse of hyperthyrotrophinaemia (cases 12 and 13; fig 1B), concentrations of serum thyroid stimulating hormone were >17 mU/l at 5·9 years (case 12) and 5·4 years (case 13), but concentrations of serum thyroxine, triiodothyronine, and free thyroxine were within the normal ranges throughout the follow up period. Group C (cases 14–16; fig 1C) developed small diffuse goitres (2–3 cm width) at the ages of 3 years (case 14), 4·1 years (case 15), and 5·3

Table 2 *Initial results of thyroid function tests in patients with transient infantile hyperthyrotrophinaemia at 2 to 7 weeks of age*

Case No	*Age (weeks)*	*Thyroid stimulating hormone (mU/l)*	*Thyroxine (nmol/l)*	*Free thyroxine* (pmol/l)*	*Triiodothyronine (nmol/l)*	*% Basal metabolic rate*	*^{123}I uptake (3 hours)*
1	3	43·0	190	47·3 (G)	3·35	−3	17·7
2	3	19·5	110	35·9 (G)	3·21	+10	21·8
3	7	22·0	141	11·3 (A)	3·69	ND	ND
4	4	19·7	128	49·1 (G)	2·90	−11	ND
5	4	29·7	209	22·1 (G)	3·84	−10	36·6
6	3	18·4	217	29·7 (G)	4·09	+6	26·4
7	5	23·6	97	13·2 (A)	3·20	+16	28·3
8	5	24·1	146	21·2 (A)	3·13	ND	ND
9	5	27·0	136	20·5 (A)	3·43	ND	ND
10	3	18·3	129	ND	3·59	+4	ND
11†	5	26·4	141	14·7 (A)	4·93	ND	ND
12‡	2	29·4	160	23·5 (G)	3·89	−1	36·4
13‡	3	22·4	186	32·1 (G)	3·32	−8	31·6
14§	5	17·2	156	44·6 (G)	2·93	−12	37·6
15§	5	33·3	133	21·2 (A)	3·61	−5	26·1
16§	3	77·4	195	23·1 (A)	3·21	+14	ND
Normal range		2·8–12·0	90–187	22·8–47·2 (G) 8·08–25·5 (A)	2·43–4·52	−15 to +15	10·0–35·0

ND: not done.
*Gamma Coat RIA (G) or Amerlex Free T4 RIA (A).
†Child with hearing disturbance; ‡child with relapsed hyperthyrotrophinaemia; §child with goitre that appeared later.

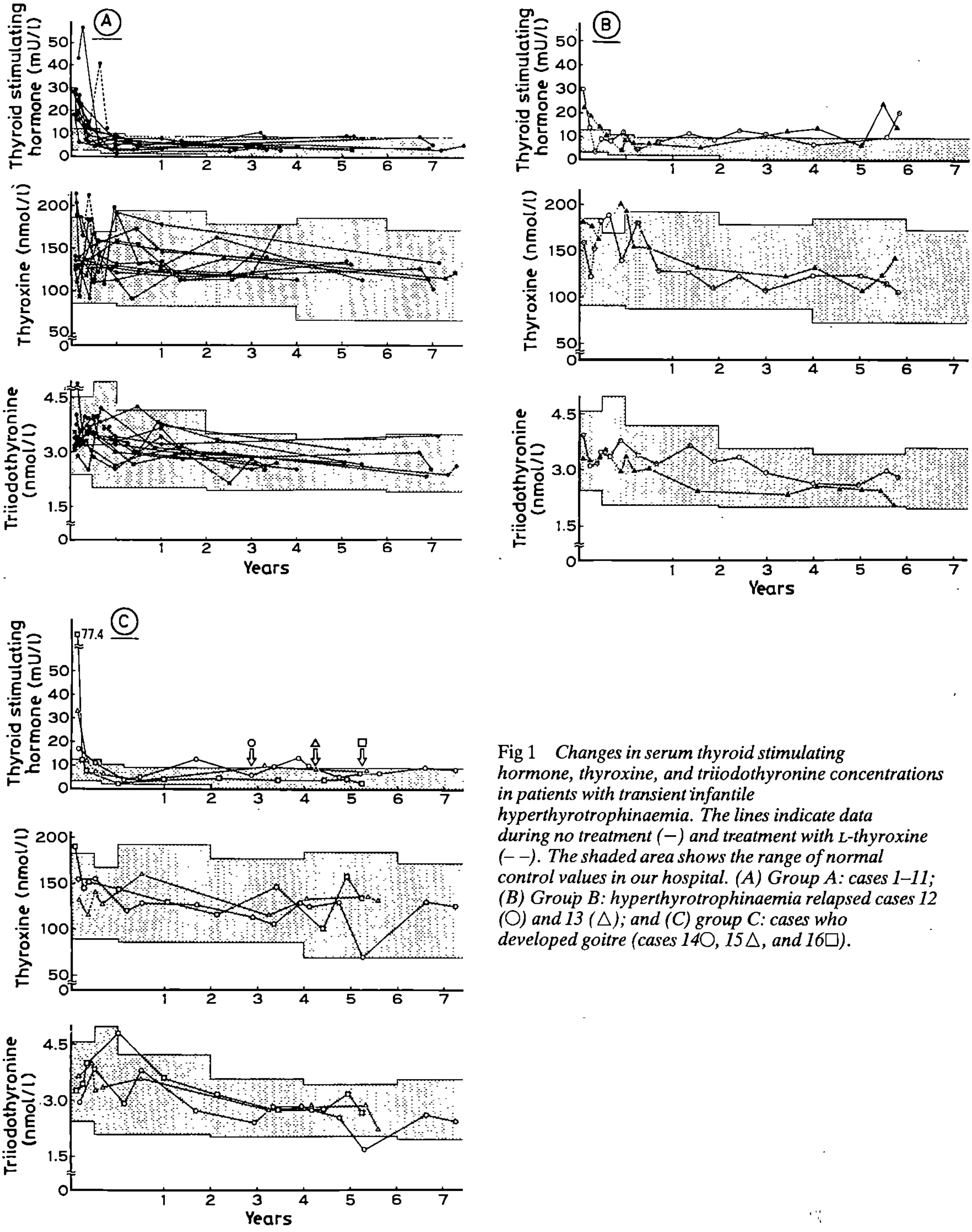

Fig 1 *Changes in serum thyroid stimulating hormone, thyroxine, and triiodothyronine concentrations in patients with transient infantile hyperthyrotrophinaemia. The lines indicate data during no treatment (—) and treatment with* L*-thyroxine (– –). The shaded area shows the range of normal control values in our hospital. (A) Group A: cases 1–11; (B) Group B: hyperthyrotrophinaemia relapsed cases 12 (○) and 13 (△); and (C) group C: cases who developed goitre (cases 14○, 15△, and 16□).*

Table 3 *Most recent results of thyroid function tests in patients with transient infantile hyperthyrotrophinaemia*

Case No	*Age (years)*	*Thyroid stimulating hormone (mU/l)*	*Thyroxine (nmol/l) (nmol/l)*	*Free thyroxine* (pmol/l)*	*Triiodo-thyronine (nmol/l)*	*Developmental quotient‖ or IQ*
1	7·1	3·5	133	21·2	3·38	119 (T)
2	6·9	4·1	114	22·2	2·60	97 (T)
3	7·0	5·8	105	22·1	2·60	99 (W)
4	7·6	5·4	124	19·9	2·66	116 (W)
5	5·4	8·7	117	16·7	2·75	90 (T)
6	5·1	4·4	136	19·9	3·07	110 (T)
7	5·3	10·8	127	21·2	3·04	120 (T)
8	3·3	4·5	142	19·9	2·70	127 (T)
9	4·0	5·6	119	25·0	2·72	133 (T)
10	3·2	4·7	121	21·8	2·67	150 (T)
11†	3·5	4·0	183	17·9	2·87	80 (T)
12‡	5·9	20·0	105	18·6	2·75	107 (T)
13‡	5·7	13·6	144	23·1	1·90	112 (W)
14§	7·1	7·6	127	21·2	2·40	110 (W)
15§	5·6	6·1	135	18·6	2·17	110 (T)
16§	5·2	2·6	137	23·1	2·61	126 (T)
Normal range		<1–9·0	73–187	9·2–27·7	1·89–3·50	

*Amerlex Free T_4 RIA.
†Child with hearing disturbance; ‡child with relapsed hyperthyrotrophinaemia; §child with goitre that appeared later.
‖Tsumori-Isobe (T) or Wechsler intelligence scales for children (W).

years (case 16). Concentrations of serum thyroxine, triiodothyronine, free thyroxine, and thyroid stimulating hormone were within the normal range except for case 14 who showed a transiently low triiodothyronine concentration at 5·1 years with slight increases in concentrations of thyroid stimulating hormone at 1·7 and 3·9 years.

Thyroid antibodies were not detected in any infant throughout the follow up period. The response of thyroid stimulating hormone to thyrotrophin releasing hormone (10 μg/kg bodyweight; TRH–Tanabe) was examined in some cases in early infancy (1–3 months of age), later infancy (6–12 months of age), and childhood (3·4–7·7 years of age); the results are shown in fig 2. In the seven infants studied in group A, peak thyroid stimulating hormone concentrations in childhood (mean (SD) 33·5 (7·5) mU/l) were significantly lower than those in early infancy (81·3 (49·1) mU/l) ($p<0·05$). Both infants in group B and one infant in group C (case 14) had significantly higher peak thyroid stimulating hormone concentrations in later infancy and childhood than found in normal controls.

The ratio of the increments in thyroid stimulating hormone (TSH) and triiodothyronine (T_3) after stimulation by thyrotrophin releasing hormone (ΔT_3:ΔTSH) of all cases examined in group A (mean (SD): 1·9 (1·5)$\times 10^3$ nmol/mU) were similar to those in normal controls (2·9 (1·8)$\times 10^3$ nmol/mU) in early infancy.

All cases showed normal growth and none were below −1·5 SD for height or weight in normal Japanese children. Bone maturation was also normal in all cases. Developmental quotient or IQ values for all infants were above 90, except for the one child who was deaf who had a score of 80 (table 3).

Discussion

In this paper we have proposed a definition of transient infantile hyperthyrotrophinaemia that is a modification of our previous definition.[2] On the basis of these criteria we found 16 cases in 281 468 newborn babies screened and estimate the incidence of this syndrome to be about 1:17600. During follow up for two to seven years, 11 children (group A) had consistently normal thyroid function and no signs or symptoms of hypothyroidism. The peak values of thyroid stimulating hormone after administration of thyrotrophin releasing hormone decreased gradually with age, becoming almost normal by the ages of 3–7 years.

The results for the ΔT_3:ΔTSH ratio after thyrotrophin releasing hormone indicate that these children respond to endogenous thyroid stimulating hormone, and compensated primary hypothyroidism can be excluded as the residual capacity of the thyroid to secrete triiodothyronine after thyroid stimulating hormone stimulation was the same as that in age matched normal controls. In this respect, transient hyperthyrotrophinaemia can be

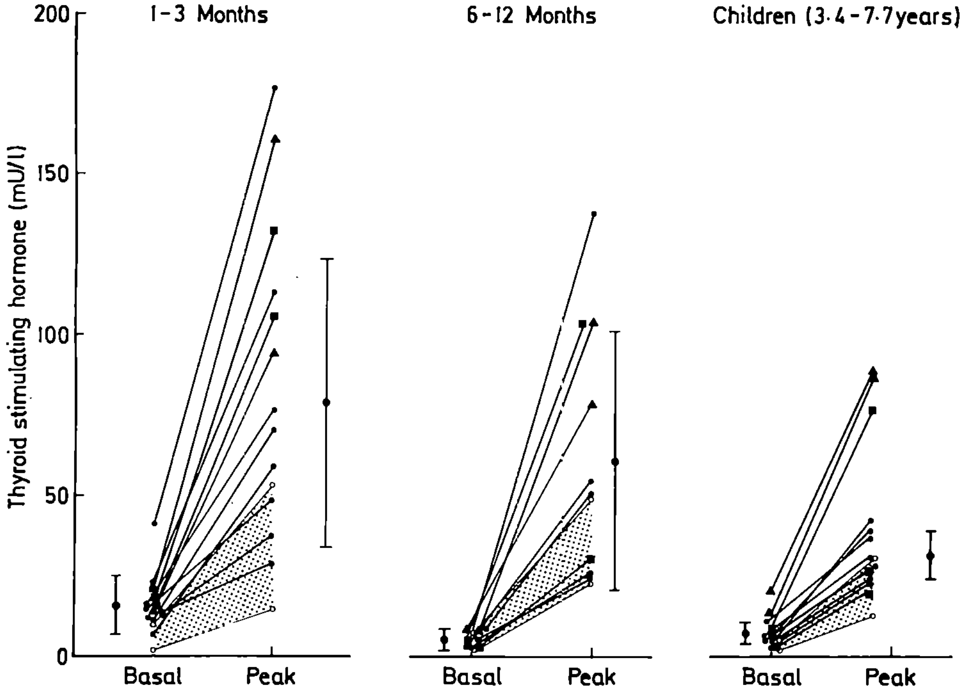

Fig. 2 *Thyroid stimulating hormone response to thyrotrophin releasing hormone stimulation test in group A (●), B (▲), and C (■). the shaded area shows the range of normal control values. Closed circle with vertical bars indicate means (SD) of thyroid stimulating hormone concentrations of group A cases. Peak thyroid stimulating hormone values of group A cases in childhood were significantly lower than those obtained in early infancy ($p<0\cdot05$).*

considered to be a different condition from primary hypothyroidism. The children in group A may have had some form immaturity of the hypothalamic-pituitary-thyroid axis—probably in the negative feedback system—in early life, but this immaturity had disappeared by childhood.

On the other hand, two children in group B showed relapse of hyperthyrotrophinaemia and in three children in group C small soft diffuse goitres developed. The children in group B had slightly higher concentrations of serum thyroid stimulating hormone than normal. We have followed up these cases without medication, and they show good psychosomatic development with normal bone maturation. The reason for hyperthyrotrophinaemia in these cases is unknown. If their concentrations of serum thyroxine decrease in response to increased demands for thyroid hormones in the future, they will have a final diagnosis of mild primary hypothyroidism. On the other hand, if their thyroid stimulating hormone is maintained at a raised concentration or fluctuates without any abnormalities in the concentration of serum thyroid hormones, we may classify them as having sustained or fluctuating hyperthyrotrophinaemia.

One child in group C had a persistently exaggerated thyroid stimulating hormone response to thyrotrophin releasing hormone and one episode of a low triiodothyronine and a low-normal thyroxine concentration. The ^{123}I scinitigram of this girl showed normal location but slight enlargement of the thyroid, and her ^{123}I thyroidal uptake was normal with no discharge of ^{123}I by thiocyanate; mild hypothyroidism due to a defect of hormone synthesis still cannot be excluded in this girl. The other two children (cases 15 and 16) had small soft goitres but their serum thyroid hormones and thyroid stimulating hormone concentrations were normal. These children most likely had diffuse simple goitres. As these three children show good physical and mental development and normal bone maturation, we will continue their follow up without treatment.

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References

1. Miyai K, Amino N, Nishi K, *et al.* Transient infantile hyperthyrotrophinaemia. Report of a case. *Arch Dis Child* 1979;**54:** 965–7.
2. Miyai K, Harada T, Nose O, *et al.* Transient infantile hyperthyrotrophinemia. In: Stockist JR, Nagataki S, eds. *Thyroid research VIII.* Canberra: Australian Academy of Science, 1980:33–6.
3. Miyai K, Harada T, Nose O, Mizuta H, Amino N, Yabuuchi H. Hyperthyrotrophinaemia with normal thyroid hormone concentration in newborn babies. In: Naruse H, Irie M, eds. *Neonatal screening. International Congress Series 606.* Amsterdam: Excerpta Medica, 1983:44–9.
4. Wada Y. Research on mass screening system. *Annual Report of the Health and Welfare Ministry in 1986 on developmental disturbance.* Tokyo: Health and Welfare Ministry, 1986. (In Japanese).
5. Miyai K, Oura T, Kawashima M, *et al.* A new method of paired thyrotropin assay as a screening test for neonatal hypothyroidism. *J Clin Endocrinol Metab* 1978;**47:**1028–33.
6. Smith DW, Klein AM, Henderson JR, Myrian Thopoulos NC. Congenital hypothyroidism—signs and symptoms in the newborn period. *J Pediatr* 1975;**87:**958–62.
7. Tsumori S, Inage K. *Diagnostic method of psychomotor development in infants and young children.* Tokyo: Dainihon Tosho, 1961. (In Japanese.)
8. Wechsler D. *Wechsler intelligence scales for children.* New York: Psychological Corporation, 1949. (Kodama H, Shinagawa F. *The Japanese Wechsler intelligence scales for children.* Tokyo: Nihon Bunka Kagakusha, 1953. In Japanese.)
9. Nose O, Harada T, Maki I, *et al.* Usefulness of basal metabolic rate to monitor thyroid hormone action on peripheral tissue in neonatal hypothyroidism screened by mass screening program. In: Naruse H, Irie M, eds. *Neonatal screening. International Congress Series 606.* Amsterdam: Excerpta Medica, 1983:152–3.

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Calcium intake and cows' milk free diets

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SUMMARY In children with atopic eczema on elimination diets, the calcium intake was below the estimated requirement in 15 out of 20 who avoided cows' milk and received no milk substitute, and in three out of 26 who avoided cows' milk but were provided with a soya or casein hydrolysate formula.

Intolerance to food is sometimes suspected in children with eczema and other atopic diseases, and such children are frequently treated with a diet which excludes cows' milk. As dairy products are the major dietary source of calcium, a milk substitute based on soya or casein hydrolysate formula is usually advised to ensure an adequate intake of calcium.

The question arises as to whether in practice adequate calcium intakes are achieved in children on cows' milk free diets. In order to assess whether children on elimination diets are receiving an adequate intake of nutrients, we have used dietary surveys to examine their calcium and vitamin D intake.

Patients and methods

Between 1981 and 1987, 56 diet surveys were performed on 48 children between the age of 8 months and 14 years. All were patients with atopic eczema attending our outpatient department. All had been treated with a 'few food' or elemental diet. In the 'few food' diet the patient was allowed only six foods (for example, lamb, potato, rice, rice crispies, pears, and water) for a six week period. In the elemental diet the patient's intake consisted solely of an elemental formula (Vivonex, Norwich Eaton Laboratories) for four weeks. At the end of either period the diet was abandoned if there had not been substantial improvement in the eczema. If the eczema improved, then single food items were reintroduced at the rate of one per week with the aim of identifying foods which worsened the eczema. After three months of reintroductions, a diet survey was routinely performed to assess the nutritional adequacy of the child's diet. In eight patients the child remained on a very restricted diet for more than six months, so a diet survey was repeated. To perform a diet survey, the parents were asked to record, using household measures, all food and drink consumed during a five day period. From each record, estimated weights of food were used to calculate nutrient intake, using standard British food tables[1] and manufacturers' data. Before August 1983 this was done using a electronic calculator. Thereafter the task was performed using the Salford University 'Microdiet' programme on a microcomputer.

For this study, the patients were allocated to three groups. These were group 1: those taking cows' milk and other cows' milk products, but with other dietary restrictions; group 2: those on a cows' milk free diet and other dietary restrictions, but taking a cows' milk substitute (Wysoy (Wyeth) a soya-based formula or Pregestimil (Mead Johnson), a casein hydrolysate milk formula, or goats' milk); group 3: those on a cows' milk free diet and other dietary restrictions but taking no cows' milk substitute.

Royer noted that the adult human skeleton contains approximately 1 kg of calcium more than that of the newborn.[2] The average accretion rate from birth to 18 years is therefore around 150 mg per day. This is higher at times of rapid somatic growth, from birth to 2 years and during puberty.[2–4] Assuming an obligatory urine loss of one to six mg per day and a maximal calcium absorption from the gut of around 60%,[2] the minimum daily intake which will ensure normal skeletal mineralisation at different ages can be calculated and is shown in the table. The calcium requirements shown in the table were chosen as cut off points for a low calcium intake in the present study. A low intake of vitamin D was arbitrarily defined as less than 1 μg per day.

Results

The children on a diet including cows' milk (group 1) were found to have a mean calcium intake of 792 mg/day (range 431–1021). Those using a cows' milk substitute (group 2) had a mean intake of 413 mg/day (range 164–797), and the children in group 3, taking neither cows' milk nor a milk substitute, Table *Calcium accretion rate and requirements by age and number of patients with intake below age related requirements*

Age (years)	*Accretion rate*[2–4] *(mg/day)*	*Approximate requirements (mg/day)*	*No below requirements for age group*		
			Group 1	*Group 2*	*Group 3*
0–1	190	300	0/2	2/6	3/5
2–7	70	150	0/3	0/18	2/12
8–10	140	250	—	1/2	3/3
11–18	250	500	1/5	—	—
Total			1/10	3/26	8/20

Group 1: taking cows' milk, group 2: on milk free diet plus a milk substitute, group 3: on milk free diet with no milk substitute.

had a mean calcium intake of 213 mg/day (range 123–444). The calcium intakes in the three groups were significantly different ($p<0{\cdot}005$, Wilcoxon rank sum test).

When the calcium intake was compared with the age related requirements, however, it was found (see table) that most children studied were aged 2 to 7 years, when calcium requirements are relatively low. Thus only three of the 26 patients receiving milk substitutes had an intake lower than their requirements, while eight of 20 who were not receiving milk or a milk substitute had an intake lower than their requirements.

In the children in group 1, the mean contribution of milk to the daily calcium intake was 405 mg (51%), and a further 146 mg (18%) was derived from milk products such as cheese. A milk substitute contributed a mean of 229 mg (55%) to the daily calcium intake of the children in group 2.

The daily vitamin D intake was less than 1 μg in three out of 10 patients in group 1, seven out of 26 in group 2, and 15 out of 20 in group 3.

Discussion

This study shows that it is unsafe to assume that calcium requirements will be adequately provided by the prescription of a cows' milk substitute in children on a diet excluding cows' milk. The need for calcium supplements in such patients will depend on the calcium content of the remaining diet, the age of the child, and the nature of the disease being treated. In children with atopic eczema, there are three special circumstances which may increase the need for calcium. Firstly, intestinal absorption of calcium may be impaired in eczematous children who have an enteropathy.[5] Secondly, the absence of lactose in the diet may reduce calcium absorption.[6] Finally, there is a risk of vitamin D deficiency and consequently diminished gastrointestinal calcium absorption in children with atopic eczema who are kept out of sunlight.

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References

[1] Paul AA, Southgate DAT. *McCance and Widdowson's The composition of foods.* Fourth revised and extended edition of MRC Special Report No 297. London: HMSO, 1978.

[2] Royer P. Growth and development of bony tissues. In: Davis JA, Dobbing J. eds. *Scientific foundations of paediatrics.* 2nd ed. London: Heinemann, 1981:565–89.

[3] Ziegler EE, Fomon SJ. Major minerals. In: Fomon SJ, ed. *Infant nutrition.* 2nd ed. Philadelphia: WB Saunders, 1974:267–97.

[4] Leitch I, Aitken FC. The estimation of calcium requirement: a re-examination. *Nutrition Abstracts and Reviews* 1959;**29:** 393–411.

[5] Walker-Smith J, Harrison M, Kilby A, Phillips A, France N. Cows' milk sensitive enteropathy. *Arch Dis Child* 1978;**53:** 375–80.

[6] Zeigler EE, Fomon SJ. Lactose enhances mineral absorption in infancy. *J Pediatr Gastroenterol Nutr* 1983;**2:**288–94.

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Absence of Y specific DNA sequences in two siblings with 46XX hermaphroditism

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SUMMARY We report two siblings with 46XX hermaphroditism in whom we were unable to show the presence of Y specific DNA sequences using the DNA probes Y-190, GMGY-7, pHY2.1, pDP34, and 27a. We conclude that an autosomal or X chromosome gene mutation is the most likely mechanism of inheritance in this family with 46XX hermaphroditism.

DNA probes for regions of the Y chromosome have led to identification of Y specific DNA in 46XX and 45XO males, and to the presence of small deletions of the short arm in 46XY females with gonadal dysgenesis.[1] Thus the discordance between karyotype, phenotype, and gonadal histology can be explained by invoking translocation or deletion of a critical segment of the Y short arm, which carries male determining information, the so called testis determining factor. Recently a candidate gene for testis determining factor has been isolated.[2]

We describe two siblings who are 46XX hermaphrodites and in whom we were unable to identify the presence of Y derived DNA using five different Y specific DNA probes.

Case reports

CASE 1

Case 1 was the first child of unrelated parents. Ambiguous genitalia with hypospadias, a bifid scrotum, and bilateral scrotal gonads were noted at birth. Investigations showed a 46XX karyotype. Three injections of human chorionic gonadotrophin (1000 units) at 3 months of age resulted in a rise in plasma testosterone from 4·1 nmol/l to 6·0 nmol/l. Laparotomy showed no Mullerian structures. A gonadal biopsy specimen showed bilateral ovotestes, and gonadal fibroblast chromosomes were 46XX. Because of the well formed male external genitalia, the absence of female internal genitalia, and the plasma testosterone response to human chorionic gonadotrophin it was decided to rear the child as a male. At 3 years of age the ovarian component of the ovotestes was excised and the hypospadias repaired.

CASE 2

Case 2 was the second child in the family. His external genitalia were similar to those of his brother, as were the findings at laparotomy. Chromosome analysis showed a 46XX karyotype. Three injections of human chorionic gonadotrophin (1000 units) produced a rise in plasma testosterone from 2·0 nmol/l to 5·2 nmol/l. This child has also been raised as a male and had his hypospadias repaired and the ovarian component of his ovotestes resected at 4 years of age.

The mother of both children is healthy; the father is said to be healthy, but was not available for study.

Methods

DNA was extracted from 10 ml blood from each patient by standard methods. 5 μg DNA was digested with appropriate restriction endonuclease (Northumberland Biologicals) using buffer provided by the manufacturer. DNA was separated by electrophoresis on 0·8% agarose gel and transferred to a nylon filter (Hybond N Amersham) by blotting. The filters were hybridised for 16 hours at 65°C at a final salt concentration of 0·6 M. The probes were labelled by the random priming method and added to the hybridisation solution at a concentration of 10^6 dpm/ml. After hybridisation, filters were washed with sodium chloride/sodium citrate solution at 65°C to remove unhybridised probe, then exposed to Kodak XAR5 autoradiographic film with intensifying screens at −70°C for one to five days. Before reuse filters were washed with boiling 10 mM TRIS, pH 8.

HYBRIDISATION PROBES

Y-190[3] and GMGY-7[3] are highly repetitive probes from the short arm of the Y chromosome. pHY2.1 (DYZ2) is a very highly repetitive probe from the long arm of the Y chromosome. pDP34 is a single copy probe on the short arm of the Y with a homologous sequence in the middle of the long arm of the X chromosome[3]; 27a is a conserved and Y chromosome unique locus near to testis determining factor.[4]

Results

The figure (a) shows the results obtained with Taq1 digest and probe 27a. Only track 2 (from a normal male control) showed any hybridisation. The lack of hybridisation makes it extremely unlikely that testis determining factor was present.

The figure (b) shows the results of hybridisation of Y–190 to a TaqI filter. Again only the track from the normal male control showed hybridisation. This confirms the lack of Y chromosome material in these children. It also rules out the possibility of mosaicism as the highly repetitive Y–190 sequences would have been detected even if only 1% of 46XY cells had been present.

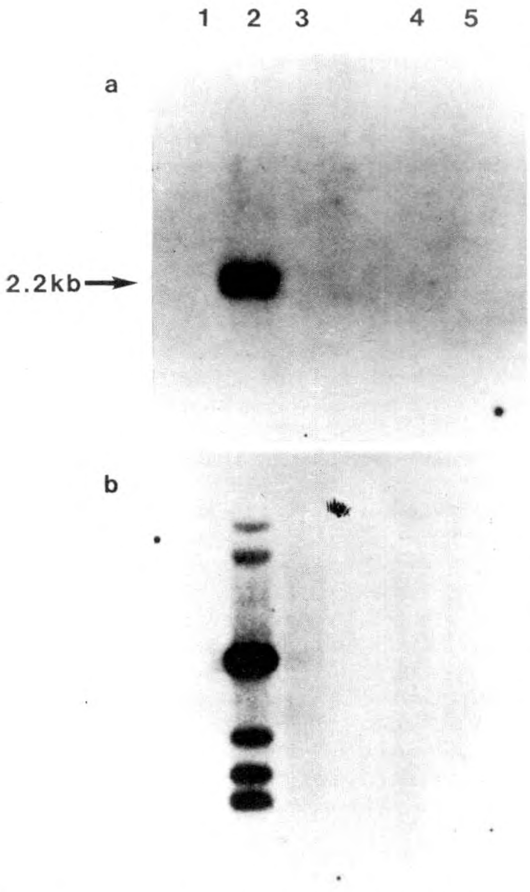

Figure *(a) Autoradiograph of filter of TaqI digest hybridised with probe 27a. (b) Autoradiograph of filter of TaqI digested DNA hybridised with Y–190. Track 1=normal female; track 2=normal male; track 3=mother; track 4 and 5=cases 1 and 2.*

The other three probes gave the same results; this confirmed the above findings (results not shown).

Discussion

Most cases of true hermaphroditism are sporadic but there have been a few reports of familial hermaphroditism.[5 6] As in our patients, some of these cases have been characterised by the presence of bilateral ovotestes, absent Mullerian derivatives, and 46XX karyotypes. In theory, sex chromosome mosaics or chimeras, translocations of part of the Y chromosome to the X chromosome or an autosome, or an autosomal gene mutation could all lead to hermaphroditism. Mosaicism and chimerism are unlikely in our cases, however, because of the familial nature of the condition, the absence of cytogenetic evidence of a 46XY cell line in the gonadal fibroblast cultures, and the inability of the DNA probes to detect a 46XY cell line in peripheral lymphocytes. A DNA probe coding for a gonadal determining factor has recently been isolated.[2] The probe, 27a, used here is extremely close to gonadal determining factor on the Y chromosome, and therefore a translocation of gonadal determining factor is unlikely in view of our inability to detect any 27a fragments.

A gene mutation on an autosome or X chromosome is a much more likely explanation for our patients' familial hermaphroditism. Such a mutation could result in differentiation of a testis or ovotestis in a subject with a 46XX karyotype and in the absence of a Y chromosome. In the female heterozygous state the mutation would be insufficient to induce the indifferent gonad to become a testis but in the homozygous state ovotestes or a testis could differentiate. As there is a sequence closely related to gonadal determining factor on the X chromosome[2] models have been suggested in which gonadal differentiation is determined by the dosage of factors from the X and Y chromosomes.[7] Unusual families such as these will provide the material to test such hypotheses.

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References

[1] Affara NA, Ferguson-Smith MA, Magenis RE, *et al.* Mapping the testis determinants by an analysis of Y-specific sequences in males with apparent XX and XO karyotypes and females with XY karyotypes. *Nucleic Acids Res* 1987;**15**:7325–41.

[2] Page DC, Mosher R, Simpson EM, *et al.* The sex determining region of the human Y chromosome encodes a finger protein. *Cell* 1987;**51**:1091–104.

[3] Pearson PL, Kidd KK, Willard HF. Report of the committee on human gene mapping by recombinant DNA techniques. *Cytogenet Cell Genet* 1988;**46**,331–81.

[4] Pritchard CA, Goodfellow PJ, Goodfellow PN. Isolation of a sequence which maps close to the human sex determining gene. *Nucleic Acids Res* 1987;**15**:6159–69.

[5] Clayton GW, Darrel Smith J, Rosenberg HS. Familial true hermaphroditism in pre and post pubertal genetic females. Hormonal and morphological studies. *Journal of Clinical Endocrinology* 1958;**18**:1349–58.

[6] Skordis NA, Stetka DG, MacGillivray MH, Greenfield SP. Familial 46XX males coexisting with familial 46XX true hermaphrodites in same pedigree. *J Pediatr* 1987;**110**:244–8.

[7] Ferguson-Smith MA. Genes on the X and Y chromosomes controlling sex. *Br Med J* 1988;**297**:635–6.

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Psychological care of survivors of a fire

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SUMMARY A mother and daughter were the sole survivors of a house fire. Support, maintenance of the parent–child relationship, and monitoring and facilitating the grieving process in a way that was consistent with the developmental stages of the patients were the basis of management.

Case report

Four members of an Asian family of six died in a fire, started by a gas heater while they slept. They were the father, two daughters aged 11 and 2, and a son aged 9. The mother and 7 year old daughter were admitted to the intensive care unit of the district general hospital. They were both suffering from extensive heat and inhalation injuries, and required ventilatory support—the mother for several hours, and the daughter for several days, during which she was sedated and paralysed.

The mother spoke little English, and so most communication was through her local authority social worker who spoke her language. Visitors told the mother that the other members of her family were in another hospital. Three days later she was told of their deaths. She seemed numbed, shed few tears, and asked no questions. Five days after the fire, the daughter had still not been told what had happened. She played quietly with nursing staff and often seemed frightened, but asked no questions about her burns, her presence in hospital, or the whereabouts of her father, brother, and sisters. She avoided contact with her mother. The mother's father was unable to be with her for another week. Physically, mother and daughter were well enough to be transferred from the intensive care unit.

Psychological aspects of further management

Because we thought that a multidisciplinary team approach would be the best way to help the patients, the paediatrician (GS), child psychiatrist (TJ), social worker, and nursing staff met regularly. These meetings helped us to acknowledge our feelings of hopelessness and our own memories of loss. We were then more able to separate these from our thinking about the needs of this mother and daughter.

We wished to support the relationship between the mother and daughter, so we ensured that when they were transferred they went to adjacent wards so that they could spend as much time as possible together. We also attempted to support their relationship by encouraging the mother in her role as a parent. There were aspects of hospital routine which made this difficult. The authority of a mother and the authority of hospital staff sit together somewhat uneasily, particularly when both the mother and her daughter are inpatients. In this case the mother's authority was undermined when the staff, despite the reluctance of the mother (who was suffering her own psychological injury), told the daughter about the fire and the deaths.

The daughter needed to know about the fire and deaths as soon as possible to end her uncertainty, to allow her to start grieving, and to avoid her hearing inaccurate accounts from other patients. It was apparent that both mother and daughter were numbed by their experience in the fire, and that any information given to them would have to be repeated, probably several times. We went to the mother's cubicle in the intensive care unit. She seemed anxious and a little drowsy, her face extensively marked by superficial burns. She was reluctant to talk about the fire and the deaths. The daughter was brought into the cubicle. She seemed frightened and withdrawn. Her face too was covered by superficial burns. She withdrew when her mother tried to hold her. GS asked about their memories of the fire. The daughter listened intently, holding on to the nurse and saying nothing. Slowly and clearly he went through the details as far as they were known, asking further questions, all unanswered. Mother and daughter looked increasingly frightened and distressed. The daughter kept her distance from her mother. After several minutes the distress in the room became unbearable and the daughter was returned to her own bed. Members of the same small staff group discussed the fire again with them on subsequent days.

Gradually their numbness was replaced, initially by disbelief and some anger (on the part of the mother), and then by tears. The mother talked about the fire and deaths with her daughter and the two of them became physically and emotionally closer. They talked about the dead family members, crying and reminiscing. They visited the burnt out shell of their house. The daughter worked through the tragedy in her drawings which included houses and symbolic representations of fire. This grief work was accomplished by the mother and daughter with the help of relatives and the local community. The contribution of GS and TJ in meetings with the family and with the multidisciplinary team was to provide further support and reassurance that the grief process was healthy and normal.[1-3] Monitoring the progress of mother and daughter through the stages of shock, protest, and despair,[2] and noting the signs of recovery, TJ was able to confirm that more specialised help, as would be appropriate for pathological grief, was not necessary. GS, who was present at all these meetings, was able not only to add his own support and encouragement, but also to model an acceptance of the understanding and knowledge brought by TJ. These meetings also showed that the staff were working as a team, which reduced the risk of some staff being seen as good and some as bad, a phenomenon that can lead to actual conflict and splitting within the staff group.

Exploration of the daughter's understanding of death and its consequences provided a set of words and concepts, the meaning of which was known to her, and to the staff talking to her. She soon began talking about her father being in heaven and made it clear that she knew he would not be returning. Staff were then able to talk with her about her feelings concerning her dead family. Some children who are not much younger than this girl may have a different understanding of death; they may believe it to be reversible. They may worry mostly about their separation from the dead loved one, or about their belief that they have killed them by wishing them dead in an angry moment. Exploring the belief systems and particular preoccupations of a child are prerequisites to being able to help them in grief.

References

[1] Parkes CM. *Bereavement: studies of grief in adult life.* Harmondsworth: Penguin, 1986.

[2] Bowlby J. Pathological mourning and childhood mourning. *J Am Psychoanal Assoc* 1963;11:500–41.

[3] Lieberman S, Black D. Loss, mourning and grief. In: Bentovim A, ed. *Family therapy; complementary frameworks of theory and practise.* London: Academic Press, 1982.

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Neonatal pneumatosis cystoides intestinalis caused by volvulus of the mid intestine

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SUMMARY A case of malrotation of the mid intestine with volvulus is reported in an infant in whom the clinical and radiological appearances were unusual, and had led to a misdiagnosis of necrotising enterocolitis. If the correct diagnosis had been made earlier, operation might have saved the infant's life.

Volvulus of the mid intestine is a life threatening complication of intestinal malrotation with a high risk of mortality; it is common in infants who present with symptoms of malrotation.[1 2]

Case report

A 1200 g infant girl, small for gestational age, was born at 36 weeks' gestation. Apgar scores were 8 and 9 at one and five minutes. The infant did well for the first 3 days of life, feeding was begun at 24 hours of age, and was well tolerated. On the fourth day she developed bloody stools, abdominal distension, and increasing gastric residues. The initial radiographs of the abdomen showed elongated distended loops of bowel throughout the abdomen with pneumatosis cystoides intestinalis in the left upper quadrant, which were thought to indicate necrotising enterocolitis. Two later sets of radiographs also showed gaseous distension of the stomach and proximal duodenum that was unchanged over one day; the importance of the duodenal distension was not appreciated. The patient's clinical state worsened, and the intestine perforated, with evidence of pneumoperitoneum (fig). The dilatation of the duodenum was finally recognised and the diagnosis of probable volvulus of the mid intestine was made. At operation malrotation with volvulus of the mid intestine was found, with necrosis of most of the ileum and right and transverse colon. The infant died shortly afterwards.

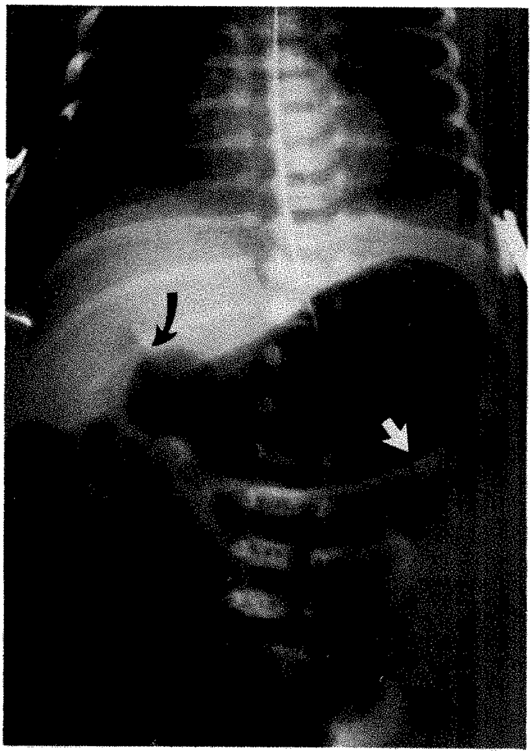

Figure *Anterioposterior view of abdomen showing duodenum dilated out of proportion to remaining bowel. There is pneumatosis cystoides intestinalis in left upper quadrant (white arrow). Pneumoperitoneum has developed secondary to bowel perforation (black arrow on falciform ligament outlined by air).*

Discussion

During normal embryological development the proximal duodenojejunal loop and the caecocolic loop independently complete counter clockwise 270° rotations along the axis of the superior mesenteric artery. During this time the mesentery of the mid intestine acquires a wide base that extends from the ligament of Treitz to the caecocolic junction and is protected from volvulus and strangulation. Intestinal malrotation is a term referring to a wide range of embryological failures of rotation and fixation of the intestine that result in the mesentery having a narrower base than normal. Abnormal peritoneal bands representing indirect attempts at fixation cross the duodenum and are a source of obstruction.

Radiological diagnosis of malrotation depends on the identification of the abnormal position of the duodenojejunal junction. This junction should lie to the left of the spine and should reach a height that approximates to the junction of the first and second parts of duodenum.[3]

Though not all patients with malrotation have symptoms, those presenting with intestinal obstruction usually do so in the first three months of life. Younger infants who present in this way are at a higher risk of volvulus and bowel necrosis than patients who present when they are older.[1 2]

Once volvulus has occurred, the sudden onset of bilious vomiting is an almost constant finding, regardless of age. Before vascular compromise has occurred the clinical examination may be misleading, as the abdomen may be soft and non-tender between episodes of pain. As vascular compromise develops, abdominal distension, tenderness, bloody stools, and eventually hypovolaemia and shock develop.[1 2]

The pattern of abdominal bowel gas in volvulus of the mid intestine is variable and can be misleading. Mucosal ischaemia can lead to the development of pneumatosis cystoides intestinalis, as in the case presented here. This event, however, is rarely reported. In our review of published reports (including 382 cases of volvulus[1 2 4 5]) only three such cases are mentioned.[2 4 5] This gas pattern can be particularly confusing in a premature infant, in whom necrotising enterocolitis is the most common cause of pneumatosis cystoides intestinalis. The present case, and the three previously reported, illustrate this problem.

Proximal duodenal obstruction is a common finding with volvulus of the mid intestine, and the amount of gas distal to the obstruction (though usually reduced) may be variable.[1 2 6] Disproportionate duodenal dilatation, however, is not seen in straightforward necrotising enterocolitis. In our review of 96 films from 26 infants with uncomplicated necrotising enterocolitis, no duodenal dilatation was seen. Our patient's clinical signs of abdominal distention, non-bilious gastric residues and bloody stools—and the additional finding of pneumatosis cystoides intestinalis on abdominal radiograph—suggested a diagnosis of necrotising enterocolitis. It was the disproportionate amount of duodenal dilatation that finally suggested the diagnosis of malrotation.

Conclusion

Bowel necrosis caused by malrotation with volvulus of the mid intestine may mimic ischaemic bowel disease such as necrotising enterocolitis. Persistent distension of the proximal duodenum should suggest the correct diagnosis and lead to early contrast examination and surgical correction.

References

[1] Potts SR, Thomas PS, Garstin WIH, McGoldrick J. The duodenal triangle: a plain film sign of midgut malrotation and volvulus in the neonate. *Clin Radiol* 1985;**36:**47–9.

[2] Berdon WE, Baker DH, Bull S, Santulli TV. Midgut malrotation and volvulus. *Radiology* 1970;**96:**375–83.

[3] Nussbaum A, Kirkpatrick JA. Malrotation of the midgut in infants and children. Part II. *Contemporary Diagnostic Radiology* 1983:**6:**4–5.

[4] Schorr S. Small-intestinal intramural air. *Radiology* 1963;**81:** 285–7.

[5] Bunton GL, Durbin GM, McIntosh N, *et al.* Necrotizing enterocolitis. *Arch Dis Child* 1977:**52:**772–7.

[6] Kassner EG, Kottmeier PK. Absence and retention of small bowel gas in infants with midgut volvulus: mechanisms and significance. *Pediatr Radiol* 1975:**4:**28–30.

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Treatment for refractory myasthenia gravis

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SUMMARY An 8 year old girl with ocular myasthenia gravis was treated with high dose intravenous immunoglobulin and high dose intravenous methylprednisolone. Ocular symptoms recurred seven months after the start of the immunoglobulin. She has been in remission for more than 12 months after two courses of intravenous methylprednisolone, and administration of oral prednisolone was discontinued.

Recently, high dose intravenous immunoglobulin and high dose intravenous methylprednisolone have been reported to improve the symptoms of generalised myasthenia gravis.[1 2] We have treated a patient with ocular myasthenia gravis refractory to several anticholinesterase compounds and oral prednisolone with pulses of intravenous immunoglobulin and methylprednisolone.

Case report

A girl (born in May 1977) started to have ptosis of the right eye at the age of 1·5 years. Clinical examination and tests confirmed ocular myasthenia gravis without thymoma and she was treated with anticholinesterase compounds. At the age of 3·5 years ptosis and diplopia worsened and prednisolone 20 mg was given on alternate days along with pyridostigmine bromide 90 mg/day and distigmine bromide 5 mg/day. The ocular symptoms were inversely correlated with the doses of prednisolone and she alternated between transient relief and aggravation of her symptoms. Treatment with anticholinesterase compounds was unsatisfactory.

At the age of 5 years ptosis and diplopia worsened during reduction of prednisolone dose (figure A). The dose of ambenonium chloride was gradually increased and administration of pyridostigmine bromide and distigmine bromide was discontinued. Treatment with ambenonium bromide was unsatisfactory and administration of prednisolone 20 mg on alternate days was again started.

At the age of 8·4 years she had a prolonged relapse and prednisolone dose was increased to 30 mg on alternate days without improvement of symptoms. Oral prednisolone 55 mg (2 mg/kg) was given on alternate days for four months, but paralysis of the extraocular muscles and ptosis of the both eyes did not improve. Because of the unfavourable effects of prednisolone she was treated with high dose intravenous immunoglobulin (figure B). The daily dose of anticholinesterase compounds and prednisolone was kept constant before and during initial immunoglobulin treatment. Improvement of the ocular symptoms began on day 4 after the start of immunoglobulin treatment and all the symptoms disappeared within 14 days. The treatment was followed by a booster infusion given every two weeks plus oral administration of prednisolone and pyridostigmine. The dose of oral prednisolone was gradually reduced to 10 mg on alternate days. However, ocular symptoms recurred seven months after the start of treatment with intravenous immunoglobulin. The booster infusion of intravenous immunoglobulin was repeated five times every two or three days. An improvement of the symptoms was not remarkable and intravenous immunoglobulin treatment was discontinued in February 1987. Doses of prednisolone and pyridostigmine were increased, but ocular symptoms did not improve.

In July 1987 she was treated with intravenous methylprednisolone because she had been treated with oral prednisolone for a long period and oral prednisolone 55 mg on alternate days did not lead to a satisfactory improvement. The improvement of the ocular symptoms was not remarkable after the initial intravenous methylprednisolone and a second course was administered. The ptosis and paralysis of the both eyes improved within the next 14 days. During her remission the daily dose of anticholinesterase medication was gradually increased and the dose of oral prednisolone was reduced. In January 1988 paralysis of downward movement of the right eye was noted, but the symptom was minimal and rapidly subsided with increasing the dose of pyridostigmine. This may indicate that the patient became responsive to pyridostigmine after treatment with intravenous methylprednisolone. In June 1988 administration of oral prednisolone was discontinued. In October 1988 she was in remission and she is now receiving pyridostigmine 130 mg/day. The antiacetylcholine receptor antibodies have occasionally increased but this increase has not been correlated with the clinical symptoms.

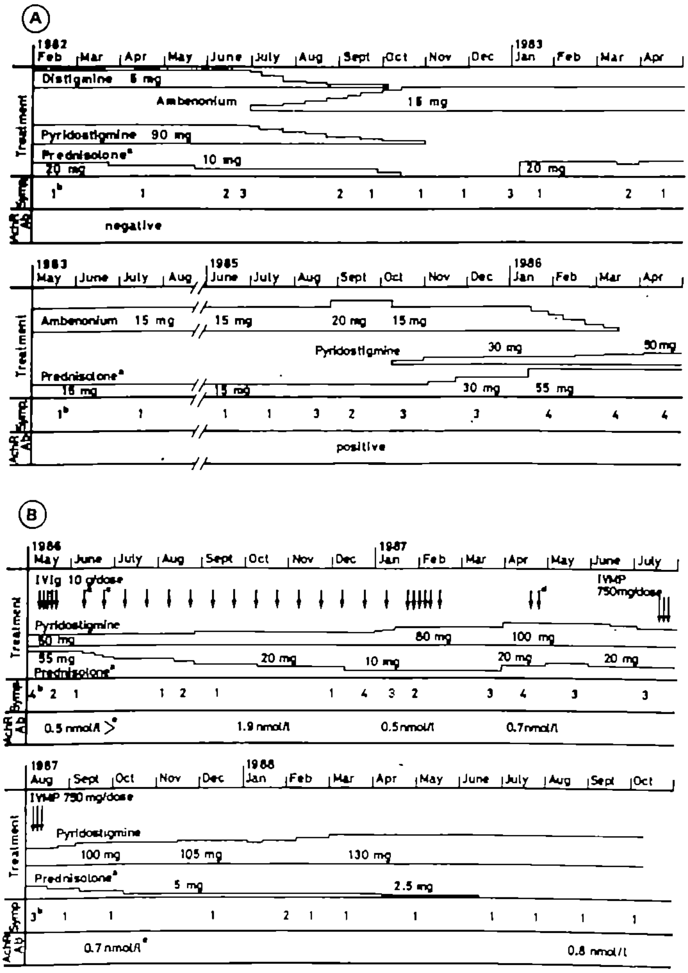

Figure *Chronological summary of clinical course before (A) and after (B) administration of intravenous immunoglobulin (IVIg) and intravenous methylprednisolone (IVMP). Polyethylene glycol treated intact 7S-immunoglobulin (Takeda) 10 g (300 mg/kg) was given as a single dose for five consecutive days and the booster infusion was repeated every two weeks. Intravenous methylprednisolone 750 mg (20 mg/kg) was given as a single dose for three consecutive days. (a) Oral prednisolone was administered on alternate days; (b) functional status: 1, asymptomatic; 2, minor symptoms (apparent in the evening); 3, mildly disabled (symptoms readily apparent, with restrictions of more demanding visual activity); 4, severely restricted in the visual activity; (c) intravenous immunoglobulin 7·5 g/dose was given; (d) intravenous immunoglobulin 5 g/dose was given for prevention of rubella; and (e) normal range of antiacetylcholine receptor (AchR) antibody is below 0·5 nmol/l.*

Discussion

We have treated a patient with ocular myasthenia gravis with five day immunoglobulin treatment followed by boosters every two weeks plus high dose intravenous methylprednisolone. As shown in the figure, both immunoglobulin and methylprednisolone were effective in ameliorating the ptosis and paralysis of the extraocular muscles, and probably in maintaining a remission for a long period. Because she had no episode of spontaneous remission during her illness, it was unlikely that the improvement of the symptoms by immunoglobulin and methylprednisolone was coincidental. The initial intravenous immunoglobulin treatment showed more rapid onset of clinical improvement compared with treatment with intravenous methylprednisolone. Ocular symptoms recurred seven months after the start of intravenous immunoglobulin, however, despite the booster infusions. Treatment with intravenous methylprednisolone followed by increasing the dose of pyridostigmine maintained her remission for more than 12 months and administration of prednisolone could be discontinued. Thus the efficacy of intravenous methylprednisolone seemed to be superior to that of intravenous immunoglobulin in our patient.

Both immunoglobulin and methylprednisolone are rather radical treatments for ocular myasthenia. Our patient had been treated with a considerable dose of oral prednisolone for a long period. Although long term corticosteroid treatment is effective in myasthenia gravis refractory to anticholinesterase compounds, side effects in children including short stature, Cushingoid appearance, hypertension, and osteoporosis are common, and attempts should be made to reduce the dose of oral prednisolone. Therefore, intravenous immunoglobulin and intravenous methylprednisolone may be useful when patients are restricted in daily activities despite prolonged administration of corticosteroids and anticholinesterase compounds.

In patients with generalised myasthenia gravis thymectomy has become increasingly recommended and this may be indicated in patients with refractory ocular myasthenia gravis. Patients with ocular myasthenia gravis do not usually require thymectomy, however, and there is no consensus that children with ocular myasthenia gravis refractory to corticosteroids and anticholinesterase medication should have a thymectomy.[3]

References

[1] Arsura EL, Brunner NG, Namba T, Grob D. High-dose intravenous methylprednisolone in myasthenia gravis. *Arch Neurol* 1985;**42:**1149–53.

[2] Arsura EL, Bick A, Brunner NG, Namba T, Grob D. High-dose intravenous immunoglobulin in the management of myasthenia gravis. *Arch Intern Med* 1986;**146:**1365–8.

[3] Olanow CW, Wechsler AS, Sirotkin-Roses M, Stajich J, Roses AD. Thymectomy as primary therapy in myasthenia gravis. *Ann NY Acad Sci* 1987;**505:**595–606.

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Controversy

Wheezy bronchitis revisited

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The description of wheezing illness in preschool children has always been confused. Terms such as wheezy bronchitis, wheeze associated respiratory illness, and asthmatoid bronchitis have been used in the past to describe episodic wheeze in infants and young children. These terms arose because it was felt by paediatricians that episodic wheeze in this age group had a more benign prognosis than asthma of older children. More recently, the use of the term asthma has been advocated to describe all wheezing illness in children, allowing no distinction between virus induced wheeze and other varieties of asthma.[1 2]

The reason for this is twofold. Firstly, in a cohort study of Australian children,[1] those who were said to wheeze only in relation to viral infections (labelled wheezy bronchitis) and those who were said to have asthma because of additional precipitating factors, both differed from the control population in terms of several atopic markers. As both wheezing groups also shared several clinical features, it was concluded that they arose from the same population and that the only difference between them was severity. Another factor that led to the abandonment of terms such as wheezy bronchitis was the clear demonstration that asthma was both underdiagnosed and inappropriately treated.[3 4] The use of terms such as wheezy bronchitis was in part held to be responsible.[3 4] Therefore, in recent years patterns of wheeze and their relationship to viral infections have seldom been defined, in either epidemiological or therapeutic studies. This practice has resulted in a loss of pathophysiological precision which may have implications that are not purely academic.

In the current issue of this journal, Clifford *et al* reporting their survey of children of 7 and 11 years,[5–7] return to the possibility that in some, recurrent respiratory symptoms could be related not to atopy but viral infections.[7] Unfortunately, despite their aim of exploring the inter-relationship of respiratory symptoms in children, they omitted to ask about the association of symptoms and viral infections.

In this article the justification for, and the implications of, classifying the syndrome of asthma in terms of clinical patterns and the response to viral infections will be presented. For want of a better term and for brevity, 'wheezy bronchitis' will be used to mean wheeze triggered by a viral infection, although it is acknowledged that this may not involve a bronchitic element. 'Asthma' will denote reversible wheezing precipitated by a number of other factors in addition to viral infections.

The natural history of asthma

Does the natural history of wheezing disorders in childhood provide evidence that such illnesses should all be labelled asthma without qualification? The pattern of wheeze in childhood, broadly speaking, can be divided into acute episodes and milder chronic symptoms.

Acute episodes, particularly in younger children, are generally considered to be induced by virus infections as they are often associated with fever and rhinitis. Viruses have been isolated in up to 42% of acute wheezing episodes.[8] Technical difficulties in viral isolation are likely to account for most of the negative results, as in one general practice survey the viral isolation rate was the same (26%) in wheezy bronchitis as in children with overt colds.[9] Typically, these acute attacks are recurrent but the frequency may vary from a single episode to repeated attacks every few weeks. There are often long symptom free periods between the acute episodes.[1] The attacks tend to decrease with age both in number and severity.

On the other hand, chronic symptoms characterised by cough and wheeze particularly at night or on exercise, unrelated to viral infections, tend to increase with age from about the age of 3 years, although they can begin earlier, and in most children symptoms have declined by puberty. These two patterns could be explained in a single population of children by frequent viral infections leading to acute attacks in younger children, with an IgE response to aero-allergens, which increases with age,[10] being responsible for 'allergic' asthma typical of older children. But most infants with episodic wheeze stop wheezing in early childhood,[1 10–13] and the prevalence of episodic wheeze has been estimated as being at least three times that of more persistent symptoms.[12] This could suggest that there are two populations of wheezers. Williams and McNichol, in their influential study of a population cohort of children, were unable to show any subgroups of wheezers when children were assessed between the ages of 7 and 10 years.[1] There are, however, possible explanations for their conclusions which are relevant to the whole debate.

Firstly, children with atopic asthma may also wheeze with viral infections. Secondly, children with wheezy bronchitis may experience nocturnal, emotional, and exercise induced symptoms, but by definition, only in association with viral infections. This could result in a failure to recognise that the precipitating factor was a viral infection. Thirdly, the children in this cohort were first seen at 7 years, an age by which many would have ceased to have episodes of wheezy bronchitis.[13]

Subsequent epidemiological studies have often failed to explore the relationship of wheezing to viral infections,[5–7 11 14] and some have attempted to explain away findings which have suggested a subpopulation of children with wheezy bronchitis.[11]

The papers by Clifford *et al* in the current issue have, at first sight, a bearing on the subject. They found that more 11 year olds were atopic but experienced less cough and non-atopic wheeze than 7 year olds. It is tempting to interpret these findings as evidence for a decline in wheezy bronchitis with age. It must be remembered, however, that Clifford *et al* compared cross sectional data at two ages and inferred age related changes. As the two populations are not necessarily comparable and there are indications that secular changes in the diagnosis or prevalence of asthma have occurred during this period,[15] their conclusions are not necessarily valid. They also showed an apparent decline in the *cumulative* prevalence of wheeze between 7 and 11 years in boys, again raising concern about the essentially cross sectional nature of the data. Nevertheless, their data are compatible with the existence in younger children of a subset with non-atopic asthma.

There is therefore some epidemiological evidence that wheezy bronchitis represents a definite subset of wheezing disease, as most children with episodic symptoms cease wheezing in early childhood and do not develop asthma. The two categories are not exclusive, however, as a proportion of children who have wheezy bronchitis in infancy will develop asthma as they grow older.

Bronchiolitis, wheezy bronchitis, and the development of asthma

Despite disfavour with the term wheezy bronchitis, clinicians have been reluctant to apply the term asthma to wheezing illness in children under 2 years. The lack of another acceptable diagnosis has led to a rather loose use of the term bronchiolitis to describe a range of disorders from a proved infection with respiratory syncytial virus in infants under 6 months to any wheezing condition in children under 2 years.[16] Bronchiolitis has characteristic features in severely affected young infants but in many cases it merges imperceptibly into wheezy bronchitis.[17] No rigid criteria have been established to separate the two conditions for epidemiological purposes. Respiratory syncytial virus infection cannot be considered the distinguishing feature as although most cases of bronchiolitis are due to respiratory syncytial virus infection, most respiratory syncytial virus infections do not result in bronchiolitis.[17]

The association between recurrent wheeze and bronchiolitis has often been described,[18 19] but despite numerous follow up studies the association between bronchiolitis and atopic asthma remains controversial.[18] Many children with atopic asthma experience wheezy bronchitis as infants so it could be said that the inexact criteria used to make the original diagnosis of bronchiolitis in follow up studies could have led to a spurious association between bronchiolitis and atopy. So what is the nature of recurrent post bronchiolitic wheezing? Unfortunately the pattern of wheezing after bronchiolitis has seldom been described in detail. Pullan and Hey found that the excess wheeze after hospital admission for bronchiolitis occurred in the first 4 years of life and was associated with little increase in atopy, and only marginal increase in bronchial responsiveness when assessed at the age of 10 years.[19] They suggest that 'a history of respiratory syncytial virus lower respiratory tract infection in infancy is associated with an excess of wheezy bronchitis but no increase in asthma'. This conclusion was then dismissed as the authors did not believe that it was valid to make a distinction between wheezy bronchitis and asthma. In a subsequent discussion of this study Pullan's summary of post bronchiolitic wheezing fits well with the present definition of wheezy bronchitis.[20]

It would seem logical therefore to consider that wheezy bronchitis and post bronchiolitic wheezing are part of the same clinical condition, namely that of a particular susceptibility to wheeze in association with viral infections. Bronchiolitis could merely be an early manifestation of this tendency. In order to show that bronchiolitis plays a causal role in either wheezy bronchitis or asthma it would be necessary to show that these conditions are increased in population cohorts of older children who were aged under 6 months during epidemics of respiratory syncytial virus. There is as yet no direct evidence that airway inflammation due to early viral infections leads to a predisposition to atopy in man, although observations from in vitro and animal studies suggest that there could be a causal link.[21]

Atopy, increased bronchial responsiveness, and wheezy bronchitis

Atopy and increased bronchial responsiveness are the two markers often found to be associated with asthma in the childhood population. Neither the possession of atopy nor bronchial hyper-responsiveness alone can explain the predisposition to wheeze, as both are found in significant numbers of children who have never had a lower respiratory illness.[2 22]

The hypothesis presented here is that there are three independent variables—viral responsiveness (an increased susceptibility to symptomatic viral infections), bronchial responsiveness, and atopic hypersensitivity—which determine the predisposition to wheeze in childhood (figure). In different combinations these interact to give rise to different wheezing syndromes. The presence of viral responsiveness and increased bronchial responsiveness leads to the condition of wheezy bronchitis; the association of atopy and increased bronchial responsiveness result in allergic asthma—for example, pollen asthma. If all three are present in the same individual then the syndrome of acute viral exacerbations on the background of chronic asthma occurs. This concept of course must be an over simplification as there is likely to be a dynamic interplay between these factors, for example between allergen exposure, atopy, and the degree of bronchial responsiveness.[23] Possibly recurrent viral infections can alter the level of bronchial responsiveness and enhance IgE sensitisation.[21] The pattern of clinical symptoms in an individual would depend on the expression of each factor at a given time. This in turn could vary with age, allergen load, environmental conditions, and level of viral immunity.

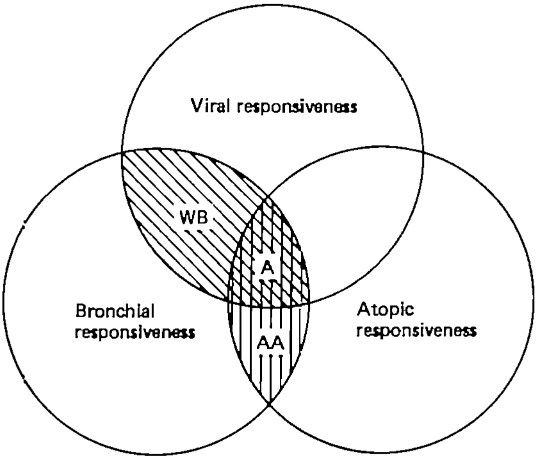

Figure *Representation of the hypothetical interaction of three factors that results in wheezing disorders in children. A dynamic inter-relationship exists between the three factors and the expression of each may vary with age and be modified by other host and environmental conditions. WB=wheezy bronchitis, AA=atopic asthma, A=asthma precipitated by both viruses and allergens.*

So if wheezy bronchitis is to be considered as a separate entity, it must be shown that a subgroup of children wheeze only in response to viral infections who have little or no atopy compared with children with asthma of the same age. Australian[1] and British[24] studies have compared the prevalence of atopy in wheezy bronchitis and asthma. In both the skin test positivity rate in those with wheezy bronchitis was intermediate between non-wheezing children and those with asthma. In both studies classification took place rather young for all potential cases of childhood asthma to be clinically identified. In addition, the full potential of the wheezy bronchitis group to have become atopic with increasing age was not assessed in the British study.[24] The Australian cohort was reassessed at 14 years,[25] but by this time the method of classification had changed and a retrospective review of those with wheezy bronchitis was not possible. Almost all children in the cohort who had ever wheezed, however, were said to have at least one laboratory indicator of allergy but these included eosinophilia and total serum IgE for which a discriminant value with which to distinguish asthma from asymptomatic controls could not be found. In many children the detection of atopy occurred many years after wheezing ceased. Persistent more severe asthma was said to be associated with allergic manifestations at a younger age.

The limited data so far available are compatible with the theory that those described as having wheezy bronchitis on clinical grounds have less atopy, or develop evidence for it later, than those diagnosed as asthmatic. Distinction between the groups must be made retrospectively in older children as laboratory detection of specific IgE precedes atopic symptoms.[10] Atopic symptoms generally increase with age throughout childhood but wheezy bronchitis is characteristically a condition of yonger children.

Recent studies have shown that bronchial responsiveness is increased in most atopic children with asthma,[7 22] and this results in symptoms after exposure to a number of agents. However, the association between wheezy bronchitis and bronchial responsiveness is not clear. Clinical observations suggest that many children experience exercise induced symptoms during attacks of wheezy bronchitis but not between acute episodes. Young children with recent symptoms of wheezy bronchitis had increased exercise lability.[26] In a comparative study Horn and Gregg found the number of children with wheezy bronchitis who had exercise induced bronchoconstriction (16%) to be far less than those with asthma (76%) but greater than controls (0%).[27] The results of retrospective studies of older children with a history of viral respiratory illness in infancy have varied with some finding increased bronchial responsiveness, which was independent of a family or personal history of atopy, even in those who were asymptomatic.[28] This has not been confirmed by others.[29]

Even though the children were as old as 7 and 11 years, the findings of Clifford *et al*[5–7] to some extent support the hypothesis that the interaction of three factors determines the clinical pattern of wheeze (figure). They describe two subgroups of children; one was 'a discrete entity' characterised by wheeze, which was strongly related to atopy and increased bronchial responsiveness.[7] Wheeze was unrelated to atopy in the absence of bronchial responsiveness and vice versa. In non-atopic children wheeze was independent of bronchial responsiveness, although there was a tendency for respiratory symptoms in general to be related to bronchial responsiveness. The authors themselves conclude that their findings could indicate a difference between atopic wheezers and those whose respiratory symptoms are related to viral infections, in whom bronchial responsiveness might be variable. Cough without wheeze could be an indicator of viral responsiveness in the absence of bronchial hyper-responsiveness.

It is likely that in some children the level of bronchial responsiveness varies, increasing during symptomatic periods. Until prospective studies in an infant population are performed it will not be known for certain whether a degree of bronchial hyper-responsiveness is a prerequisite for the development of wheezy bronchitis or asthma. Neither is it clear whether the exercise lability noted in some young children with wheezy bronchitis[26] is a predictor of later asthma as follow up studies have not been reported.

Familial factors in wheezy bronchitis

Is there any evidence from family studies of a genetic basis to the predisposition to wheeze in association with viral infections, which could lend support to this as a clinical entity? The evidence should be sought by comparing the family histories of those who wheeze *only* with viral infections, with families of those who never wheeze with viruses (which would exclude many asthmatics). Previous comparisons between the families of those with wheezy bronchitis and asthma have been confusing in this respect. For example, in the family study of König and Godfrey wheezy bronchitis was defined simply as recurrent wheeze occurring under 4 years of age.[30] In the study of Sibbald *et al*, the wheezy bronchitis children were younger than the asthma group and some might have later developed asthma.[24] It is likely that many of their asthma group also wheezed with viruses. Not surprisingly, they failed to show wheezy bronchitis as a separately inherited entity. They did, however, find that the prevalence of wheezy bronchitis was higher in the relatives of non-atopic wheezers from either group than in the relatives of atopic children. They therefore suggested that 'the reduced predisposition to asthma of many wheezy bronchitis children may result from their failure to inherit a predisposition to atopy'. This observation is compatible with the finding of Clifford *et al*[6 7] and the hypothesis that a predisposition to develop wheezy bronchitis exists and if atopy is additionally present, asthma may develop. The common link could be bronchial hyper-responsiveness which may be lost or reduced in the absence of atopy as the child grows older.

Ronchetti *et al* suggested that children who wheezed under 5 years of age could be differentiated from those who wheezed over 5 years in terms of their adenosine deaminase phenotype.[31] From this age related data it was inferred that genotype 2:1 adenosine deaminase was normally represented in virus induced wheezers but was rare among older asthmatic children. It would be interesting to review the correlation between clinical features and adenosine deaminase phenotype using stricter clinical definitions.

The familial basis of a predisposition to wheeze with viral infections has not been adequately studied but available evidence is compatible with the proposition that it could be genetic.

Implications

EPIDEMIOLOGY

Does it matter whether wheezy bronchitis is accepted as a separate manifestation of asthma? By avoiding the term, we have been left with some inconclusive answers to important clinical questions. Without separating virus induced wheeze from other causes of asthma, exacerbating factors that may act on one and not the other could be missed. For example, environmental factors such as parental smoking may influence wheezy bronchitis and not asthma.[32] Similarly, it is possible that changes in environmental pollution or weather patterns could affect the prevalence of virus infections and the distribution of aeroallergens differently and this could be responsible for the dramatic increase in admission for acute wheeze,[15,33] unassociated with an increase in prevalence of asthma in older children.[33]

Reluctance to identify the association of wheeze with viral infection is surprising in view of the renewed interest in the association between the development of atopy and viral infections. Possible mechanisms for virus induced wheeze have recently been well reviewed,[21,34,35] and several different host or environmental factors could be responsible for the development of wheezy bronchitis including an IgE response to viral antigens.[21,34]

THERAPEUTIC

There is little doubt that wheezing at any age should be treated with adequate doses of bronchodilators and not antibiotics, with additional corticosteroids if the wheezing is severe. Controversy still remains in two important clinical areas. Firstly treatment is least satisfactory in those under 18 months old and this is the age group at greatest risk of viral infections.

The other controversy concerns the efficacy of prophylaxis for recurrent acute episodes associated with viral infections in preschool children. Personal observation suggests that in contrast to older children, this age group responds poorly. There have been suggestions that chronic but not acute symptoms respond to cromoglycate and nebulised beclomethasone,[36,37] so the reason for the disappointing results of prophylactic treatment in asthma trials in the preschool age group could be related to the failure to separate acute from chronic symptoms. Unless clinical trials start to consider the therapeutic efficacy on different patterns of symptoms separately, treatment of asthma in this age group will not be rationalised. Treatment for acute wheeze remains a problem, as clearly shown by the increasing numbers who are admitted to hospital.[15,33] Moreover, unless the characteristic insidious change in the pattern of wheezing from the acute episodes of wheezy bronchitis to the more chronic nocturnal cough and exercise induced symptoms in children who develop asthma are emphasised, many children will go undertreated.

Conclusion

The rationale for the failure to identify virus induced wheeze in recent studies of asthma[3–7,11,14,22,32] is questionable and needs re-evaluating. It does not seem very wise to extrapolate uncritically from a study of 7 year old Australian children to preschool asthmatics in the United Kingdom. From the limited data available, episodic wheezing occurring particularly in younger children cannot be completely explained by atopy and bronchial hyperresponsiveness as in older children with asthma. There is clearly a need for careful, prospective studies. In particular, clinical subgroups of wheezy young children should be defined, host and environmental factors looked for, and therapeutic approaches assessed. Perhaps a more appropriate and less emotive term than wheezy bronchitis should be agreed upon . . . . .VAW (virus-associated wheeze) or WAVE (wheeze-associated virus episode)?!

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References

[1] Williams H, McNichol KN. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J* 1969;**iv**:321–5.

[2] Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;**286**:1256–8.

[3] Speight ANP, Lee DA, Hey EN. Under-diagnosis and undertreatment of asthma in childhood. *Br Med J* 1983;**286**:1253–6.

[4] Anderson HR, Cooper JS, Bailey PA, Palmer JC. Influence of morbidity, illness label, and social, family and health service factors on drug treatment of childhood asthma. *Lancet* 1981;**ii**: 1030–2.

[5] Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. *Arch Dis Child* 1989;**64**:1118–25

[6] Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren. *Arch Dis Child* 1989;**64**:1126–32.

[7] Clifford RD, Howell JB, Radford M, Holgate ST. Association between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. *Arch Dis Child* 1989;**64**:1133–39.

[8] McIntosh K, Ellis EF, Hoffman LS, *et al.* The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J Pediatr* 1973;**82**:578–90.

[9] Horn ME, Brain EA, Gregg I, *et al.* Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979;**34**:23–8.

[10] Foucard T. A follow-up study of children with asthmatoid bronchitis with skin tests and IgE to common allergens. *Acta Paediatr Scand* 1984;**62**:633–44.

[11] Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986;**61**:642–6.

[12] Price J. Asthma in children: diagnosis. *Br Med J* 1984;**288**: 1666–8.

[13] Foucard T, Sjoberg O. Prospective 12 year follow-up study of children with wheezy bronchitis. *Acta Paediatr Scand* 1984;**73**: 577–83.

[14] Anderson HR, Bailey P, Cooper JS. Palmer JC, West S. Morbidity and school absence caused by asthma and wheezing illness. *Arch Dis Child* 1983;**58**:777–84.

[15] Anderson HR. Is the prevalence of asthma changing? *Arch Dis Child* 1989;**64**:172–5.

[16] McConnochie KM, Roghmann KJ. Bronchiolitis as a possible cause of wheezing in childhood: new evidence. *Pediatrics* 1984; **74**:1–10.

[17] Horn MEC, Brain EA, Gregg I, Yealland SJ, Inglis JM. Respiratory viral infection in childhood. A survey in clinical practice, Roehampton 1967–72. *J Hyg (Lond)* 1975;**74**:157–68.

[18] Simpson H, Mok YQ. Outcome of respiratory disease in childhood. In: Milner AD, Martin RJ, eds. *Neonatal and pediatric respiratory medicine.* London: Butterworth, 1985: 211–35.

[19] Pullan CR, Hey EN. Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncitial virus in infancy. *Br Med J* 1982;**284**:1665–9.

[20] Pullan CR. Does bronchiolitis predispose to asthma in childhood asthma? In: Macloed JM, Szefler SJ, ed. *Sustained release theophylline.* Exerpta Medica, Current Clinical Practice Services 32, 1986:40–8.

[21] Busse WW. The relationship between viral infections and onset of allergic disease. *Clinical and Experimental Allergy* 1989;**19**:1–9.

[22] Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian school children III. Effect of exposure to environmental allergens. *Clin Allergy* 1987;**17**:291–300.

[23] Durham SR, Lee TH, Shaw RJ, *et al.* Immunological studies in allergen-induced late phase asthmatic reactions. *J Allergy Clin Immunol* 1984;**74**:49–60.

[24] Sibbald B, Horn ME, Gregg I. A family study of the genetic basis of asthma and wheezy bronchitis. *Arch Dis Child* 1980;**55**: 354–7.

[25] McNichol KN, Williams H. Spectrum of asthma in children II. Allergic components. *Br Med J* 1973;**iv**:12–6.

[26] Lenney W, Milner AD. Recurrent wheezing in the preschool child. *Arch Dis Child* 1978;**53**:468–73.

[27] Horn ME, Gregg I. Role of viral infections and host factors in acute episodes of asthma and chronic bronchitis. *Chest* 1973;**63**: 44–8.

[28] Gurwitz D, Covey M, Levison H. Pulmonary function and bronchial reactivity in children after croup. *Am Rev Respir Dis* 1980;**122**:95–9.

[29] Voter KZ, Henry MM, Stewart PW, Henderson FW. Lower respiratory illness in early childhood and lung function and bronchial reactivity in adolescent males. *Am Rev Respir Dis* 1988;**137**:302–7.

[30] König P, Godfrey S. Exercise-induced bronchial lability and atopic status of families of infants with wheezy bronchitis. *Arch Dis Child* 1973;**48**:942–6.

[31] Ronchetti R, Lucarin N, Lucarelli P, *et al.* A genetic basis for the heterogenicity of asthma syndrome in pediatric ages: adenosine deaminase phenotype. *J Allergy Clin Immunol* 1984; **74**:81–4.

[32] Horwood LR, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;**75**:859–67.

[33] Storr J, Barrell E, Lenney W. Rising asthma admissions and self referral. *Arch Dis Child* 1988;**63**:774–9.

[34] Welliver RC. Viral infection and obstructive airway disease in early life. *Pediatr Clin North Am* 1983;**3**:819–27.

[35] Schroeckenstein DC, Busse WW. Viral "bronchitis" in childhood: relationship to asthma and obstructive lung disease. *Seminars in Respiratory Infection* 1988;**3**:40–8.

[36] Cogswell JJ, Simpkiss MJ. Nebulised sodium cromoglycate in recurrently wheezy preschool children. *Arch Dis Child* 1985;**60**: 736–8.

[37] Storr J, Lenney CA, Lenney W. Nebulised beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986;**61**: 270–3.

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Personal practice

Establishing a register of children with special needs

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The *Court Report* recommended that every health district should maintain a register of children with handicap.[1] These registers, however, rarely meet their stated objectives, cannot provide data readily, and even yield unlikely variations in incidence of conditions like Down's syndrome and spina bifida.[2]

The requirements of the 1981 Education Act and advances in desk top microcomputing have renewed interest in registers. O'Mahony *et al* reported their approach to setting up a register but they had only just started to record data, had not started to validate the data, and did not know whether the register was meeting its stated objectives.[3]

Northumberland health district has maintained for three years a computerised register of children aged 0–16 years with long term special needs. We report the thinking behind this register, the practical implementation and validation of the register, and the uses to which it has been put. We hope that this will promote discussion and help other districts to maintain more accurate and useful registers.

Thinking behind the register

The objectives of our register are to: (a) improve the care of individual children; (b) improve the planning of services for children; and (c) improve opportunities for research and epidemiology.

Northumberland had kept a manual register for 10 years but there was no clear policy about which children should be registered. We decided that the criterion for registration would be that the child had some 'long-term special need for multi-disciplinary help or review that can be better planned and performed by being recorded centrally. The need should arise at least in part from a physical, sensory or mental impairment or chronic illness'. In practice, most registrations are: (a) children with chronic illness; (b) children who are the subject of a 'Statement of Special Educational Need'; or (c) preschool children who already need special educational provision or help from many professionals.

The following children are *not* placed on our register:

(1) Children with congenital malformations. Congenital malformations are already recorded by the Office of Population Censuses and Surveys and most do not give rise to long term special needs.

(2) Children 'at risk of a condition'—for example, deafness, cerebral palsy, non-accidental injury. The 'at risk concept' has been largely abandoned.[4] If a health district retains it for a particular problem, names should be on a separate register with its own objectives and operational control.

(3) Children with common mild chronic conditions such as asthma, eczema, glue ear, hay fever, long sight. If the condition, by its severity or complex interaction with family factors, creates a long term special need then the child should be registered because of this need not because of the diagnosis in itself.

There are of course some children whom we are uncertain whether to register or not—for example, a child with a mild hemiplegia or a child who needs remedial reading help. Provided such grey areas are recognised, the validity of data about children who are always included or excluded is not affected.

'Diagnosis' is not a logical system of classification for it may describe a disease, medical problem, impairment, or psychological circumstance. Nevertheless the concept is very useful and we have developed a 100 category classification relevant to children with chronic problems. Each child may have up to six codes. For instance a child with Down's syndrome may be coded as Down's, fostered, complex heart disease, mental retardation, glue ear.

The concepts of impairment, disability, and handicap are more logical and consistent but the World Health Organisation coding system is complex.[5] Moreover, it was not designed for children and does not take account of age or the effects of handicap on the family. We have recorded data about impairment and disability as one research objective of the register.

Implementation

Northumberland health district has a population of 290 000 and is by area the second largest health district in England and Wales. The 4000 files of the existing manual register were examined by the community paediatrician and, using the agreed criterion for registration, 1700 children's names were placed on the new register. The data recorded about each child are shown in table 1. Coding by the paediatrician took about 100 hours and data entry by the clerical officer took about 90 hours. The time needed to add or remove children from the register and to keep up to date details of school, address, etc. is about 16 hours a year of medical time and 40 hours a year of clerical time.

The program is written in DBase 2 and runs on an Apricot PC/Xi computer. The cost in 1985 for computer, printer, and software was £3500. One of the authors wrote the program. Although it is useful if the same person has clinical and computer skills, it is not essential. It is essential, however, that the program is planned and tested by clinicians who work closely with the programmer. DBase 2 or 3 is a suitable data base because it allows data to be selected, changed, or analysed in any manner (maximum flexibility) but may be 'menu driven' for day to day running by clerical staff with no computer knowledge.

The district receives information about children who may need to be registered from neonatal units, hospital discharge summaries, hospital outpatient letters, health visitors, and the local education authority. To keep the register up to date, a list is sent every year to each school doctor to confirm or change the school which the child attends. Also, when an examination is undertaken for the 1981 Education Act, the doctor completes a form for the computer.

Table 1 *Data recorded about each child*

- Unique computer number
- Surname
- First name
- Address
- Date of birth
- Sex
- County district
- Family doctor
- School
- School doctor
- Free text description of child's main diagnoses
- Coding of above diagnoses
- Coding of impairment
- Coding of disability
- Medical provision—for example, paediatrician
- Educational provision—for example, preschool teacher
- Therapeutic provision—for example, physiotherapist
- Family provision—for example, attendance allowance
- Date of educational statement

Validation of data

Validity of data may be defined as 'An expression of whether data actually represent what they purport to'. 'Item validity' is the accuracy of individual items such as date of birth, address. 'Case validity' is the extent to which the cases agree with an independent external set of cases.[6] We shall discuss our approach to establishing case validity.

Children with mild impairments may not have been ascertained or may be judged too mild to warrant registration. Children with more severe impairments should always be registered, but how confident can a district be that it learns about all these children from hospital letters, requests from education departments, etc? Each district must establish the case validity of its register before it can be used for planning, research, or epidemiology. We have studied groups of children who should always be registered and for which there was already an independent register or for which it was easy to obtain an independent list. Table 2 shows the numbers of children on the external and Northumberland registers, the overlap, and the total number of children. For more severe impairments our register is as, or more, comprehensive than external lists. For less severe impairments such as diabetes we are not so comprehensive. For impairments such as epilepsy we do not know the validity.

For preschool children there are few independent data sets with which to compare a register. We suggest as a measure of validity the number of children, unknown to the register while preschool, who become the subject of an educational statement before age 6 years. During the last three years in Northumberland there have been only five such children, two with speech, two with learning, and one with behaviour problems.

The comparisons to assess validity were made in 1987. Since then validity has improved and the register is now known, for example, to include all children at special schools or the subject of an educational statement.

Uses to which the register is put

A register must 'live'. The more it is used and the more this use is reported back to professional staff, the more accurate and comprehensive the register

Table 2 *Comparisons of the Northumberland register with independent lists of children in certain groups*

Group of children	*External list*	*No on external list*	*No on Northumberland register*	*No overlapping*	*Total*
Duchenne muscular dystrophy	Regional muscular dystrophy register	8	8	8	8
Cerebral palsy births 1975–80	Regional cerebral palsy study	30	34	28	36
Registered blind or partial sight	Social services register	26	27	26	27
Fitted with hearing aids	North East audiology register	74	90	72	92
Spina bifida	North East spina bifida clinic	16	16	16	16
Cancer under treatment	Regional cancer register	33	26	26	33
Severe mental retardation, age >5 years	Education department	164	158	158	164
Moderate mental retardation, age >5 years	Education department	448	424	424	448
Attending language unit	Education department	16	16	16	16
Children eligible to apply to Family Fund	Family Fund register	128	202	126	204
Diabetes mellitus	Specialist diabetic nurse's list	60	57	46	68

Table 3 *Examples of uses to which the register is put*

Individual care

The names of preschool children are brought up for review by the preschool panel for children with special needs. One function of this panel is to inform the education department of preschool children likely to have special educational needs.

Preschool children with certain problems are notified to the community dental service.

Information is sent to each school doctor about children with special needs in ordinary and special schools.

Planning

Information to the principal educational psychologist enabled him to apply successfully to the Department of Education and Science for funds for a 'Portage scheme'.*

Information to a specialist health visitor and social worker helped them assess the need for and subsequently introduce a parents' support group for families with handicapped children.

Information to the social services department helped them plan further developments in their respite care service for families with handicapped children.

Information to the Spina Bifida Association enabled it to plan voluntary services in Northumberland.

Research and epidemiology

Evaluation of the health surveillance programme of preschool children in Northumberland requires regular details of children with congenital deafness, severe cerebral palsy, language delay, and mental retardation.

A regional study of cerebral palsy received information about children with cerebral palsy.

Three separate national studies of congenital rubella, autism and deaf-blind children received information about such children.

The Family Fund in York compared its register with the Northumberland register and reported the proportion of children with severe handicap who applied to the fund.

A working party of the British Paediatric Association received a report on the prevalence of disabling conditions in childhood in Northumberland.

*The Portage scheme is a home visiting service for parents of children with special needs who are under 5 years of age. It encourages home based teaching of appropriate developmental skills.

becomes. Reporting back also helps professional staff to understand how they might use the register for their own planning or projects.

Table 3 gives examples, under each objective, of uses to which the register is put. Some are local and each district will have its own requirements. Others should occur in every health district. For example, every district should monitor its preschool screening programme and will require details of profoundly deaf children to do this. All districts must also ensure that the education department is informed early of preschool children likely to have special educational needs.

Discussion

Some district registers record more data about each child than we do. We have restricted our data because:

(1) A small amount of accurate data which can be kept up to date is preferable to a larger amount of less accurate data. We also think it is not good clinical practice or use of resources to arrange regular examinations of children mainly to keep a large data set up to date.

(2) Our register was up and running within six months and has data on children 0–16 years

with special needs. Districts which record more data will usually enter only *new* children as they present. It is therefore 10 to 15 years before the full benefit of the register is realised.

(3) Large data sets tend to include more subjective information about unmet need and the extent to which social factors contribute to a need. Subjective information is essential in clinical practice but is less useful for epidemiology, research, or planning purposes.

Why use a computer at all? Could not a manual system be just as good? For each individual task a manual system is good but when many tasks are performed on a regular basis, each task needs a separate subregister to be maintained or a separate manual search made of the main register. Further, any data or text for regular circulation need to be typed each time. Finally new requests for data for planning or research require lengthy manual search and analysis. We believe that it is these constraints on regular or unforeseen analysis and reporting that have made district registers so little used and thus so inaccurate.

An important reason therefore for introducing a computerised system is to have readily available data. Facilities for this must therefore be available from the outset. Eventually the National Child Health Computing System may provide the flexibility needed for local input/output and analysis of data, but at present it does not. 'As child care is primarily a local concern, the best computer option will usually be a small local system with sound operational control on a locally co-ordinated basis'.[7] Microcomputers are now as fast and advanced as necessary to run a register of children with special needs.

We hope that districts will be encouraged to establish and use registers because they should be of immediate benefit to them. We also hope that districts will be encouraged to report and publish their developments to help us all to understand better the concepts of impairment, disability, and handicap and the practical difficulties of recording useful data about them.

Conclusion

Registers of children with special needs are held by health districts but little attention has been paid to their objectives, criteria for registration, or validity. The registers are therefore not used or trusted. Our register has clear local objectives and operational control and has run for three years. The small amount of data recorded about each child is kept up to date and used to improve opportunities for individual care, service planning, research, and epidemiology. We have argued that a simple computerised database is more appropriate than either a manual system or a more complex computer system. The uses to which a register is put must be regularly reported to the staff who contribute data so that the relevance of the register is appreciated and its accuracy thereby maintained.

References

[1] Committee on child health services. *Fit for the future.* London: HMSO, 1976. (Court report.) (Cmnd 6684.)

[2] Balarajan R, Weatherall JAC, Ashley JSA, *et al*. A survey of handicap registers for preschool children in England and Wales. *Community Med* 1982;4:315–24.

[3] O'Mahony MC, Allsop M, Heath C, *et al*. The register of children with special needs—an approach. *Public Health* 1987; **101**:9–15.

[4] Richards IDG, Roberts CJ. The 'at risk' infant. *Lancet* 1967;**ii**:711.

[5] World Health Organisation. *International classification of impairments, disabilities, and handicaps.* Geneva: World Health Organisation, 1980.

[6] Stone H. A method for the validation of data in a register. *Public Health* 1986;**100**:316–24.

[7] Dodge JS. The use of microcomputers for child health services. In: Macfarlane JA, ed. *Progress in child health.* Vol 2. London: Churchill Livingstone, 1985.

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Current topic

Lichen sclerosus

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Lichen sclerosus, previously termed 'lichen sclerosus et atrophicus', is a uncommon disease that presents to a wide variety of medical disciplines. It is a cause of much distress, not only because of its symptoms, but also, increasingly, because of a potential to be misdiagnosed as sexual abuse.[1–3] For those familiar with lichen sclerosus in childhood it is usually possible to make a firm clinical diagnosis.

The incidence of lichen sclerosus is hard to estimate as patients present to different specialties. Mild cases may never come to receive medical attention, and others may remain misdiagnosed. The disease is much less common in children than in adults: in a series of 290 cases only 20 developed the disease below the age of 16.[4] We currently have 14 girls aged 15 or under suffering from lichen sclerosus under our care in a dermatology unit serving a population of 866 000, but the incidence is probably higher than this figure would suggest.

The well established association with organ specific autoimmune disease has resulted in lichen sclerosus being regarded as an autoimmune phenomenon.[5 6] There may also be a genetic component as several familial cases and a pair of identical affected twins have been described.[3 4 7 8]

Clinical features

Onset may occur as early as 6 months of age.[9] Lichen sclerosus occurs in both sexes but is generally held to be much less common in males. Although the major clinical problem with lichen sclerosus is in females, histological evidence of lichen sclerosus (in the male often termed balanitis xerotica obliterans) can frequently be found after circumcision for scarring phimosis.[10] Lichen sclerosus should therefore always be considered in any boy presenting with this condition. Circumcision is generally curative. Lichen sclerosus has a strong predilection for the anogenital region but may affect any area of the skin.

In girls the most commonly seen pattern is involvement of both the vulva and perianal region, but the latter may be spared. When extragenital sites are affected there is usually anogenital disease also.

The appearance of the vulva is usually diagnostic. There are characteristic shiny white papules and plaques, with a semitranslucent appearance likened to mother of pearl. The affected skin usually shows a tendency to fine wrinkling giving an appearance termed 'cigarette paper skin'. In the more severe cases purpura, excoriation, blistering (usually haemorrhagic), telangiectasia, erosion, and bleeding may be present. When both the vulva and perianal region are affected the disease often takes on an 'hour glass' or 'figure of eight' pattern. (see figure).

Common presenting complaints are vulval soreness, pruritus, bleeding, and haemorrhagic blisters. Pain on defaecation and dysuria, often associated with crying and considerable distress on defaecation and micturition, are common symptoms in young patients.[11 12] The tendency to avoid micturition may cause nocturnal enuresis, nocturia, and appreciable sleep disturbance. Pain on defaecation may lead to severe constipation. Exudation and vaginal discharge may be prominent features, particularly during episodes of superinfection.

The severity of the disease varies widely. It may be virtually asymptomatic but in severe cases exacerbations develop in which the vulva becomes severely eroded, excoriated, and haemorrhagic. Dysuria and pain on defaecation can be troublesome and persistent. In its most severe form lichen sclerosus may lead to obliterative, atrophic scarring of the genitalia.

Diagnosis

There is usually little difficulty establishing the diagnosis of childhood lichen sclerosus on the basis of the clinical features described above. In our experience vulval biopsy is of no value and causes unnecessary discomfort to the patient. This is because the histology of lichen sclerosus, although characteristic, is often rather subtle, so that the

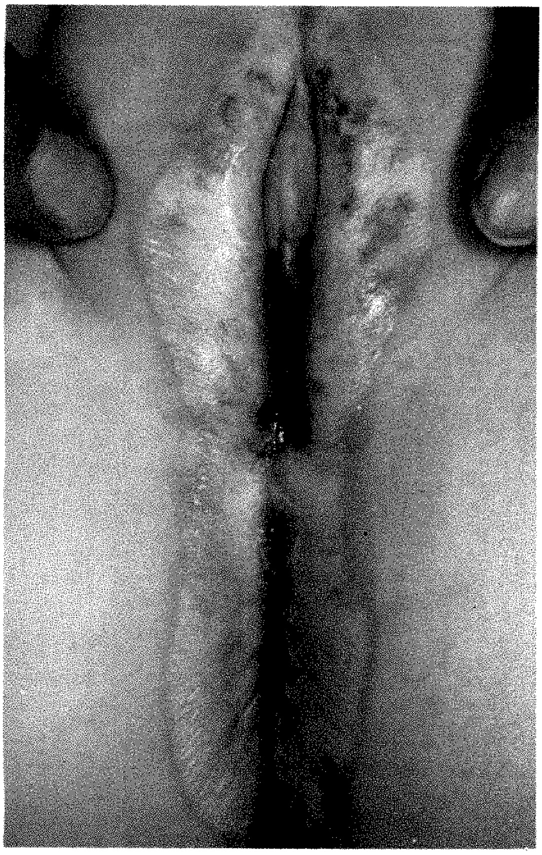

Figure *Typical 'figure of eight' pattern of anogenital lichen sclerosus.*

diagnosis may easily be missed unless already suspected clinically. The most common histological finding is a featureless band of oedematous hyalinised collagen in the upper dermis.[13] There is often a lymphohistiocytic infiltrate in the deeper dermis particularly around skin appendages such as hair follicles. Rete pegs are short or absent. The epidermis is usually atrophic, and hyperkeratosis is sometimes present. These changes are often masked during exacerbations by acute inflammatory changes due to excoriation and superinfection.

There are few conditions that can be confused clinically with lichen sclerosus in childhood. Lichen planus, although unusual, may occur at this age, but mucosal lesions are usually delicate, lace like, white striae. Lichen simplex chronicus (circumscribed neurodermatitis) is more pruritic in nature, and the lesions are poorly circumscribed areas of hyperkeratosis and excoriation lacking the specific features of lichen sclerosus. Leucoplakia is not seen in childhood.

Concern regarding sexual abuse

As severe lichen sclerosus may cause excoriation, erosion, haemorrhage, blistering, or purpura of the vulva, it is perhaps not surprising that cases have been mistaken for sexual abuse. Several such cases have been reported,[1-4] and others have undoubtedly occurred. Wallace described such a case in 1970, well before the current increased awareness of sexual abuse.[4]

It is well recognised that lichen sclerosus may develop at sites of trauma (that is, exhibit the isomorphic (Köbner) phenomenon).[4 14] It has also been claimed that a child with lichen sclerosus is 'more likely to sustain injuries after abuse'.[3] Notwithstanding these observations, it must be stated that there is absolutely no evidence to support any link between lichen sclerosus and sexual abuse. Indeed, the chances of these two problems ocurring together would seem very remote indeed.

Regrettably, we have found that concern regarding misdiagnosis of lichen sclerosus as sexual abuse is now perceived not only by doctors but also by parents of affected girls. In our experience this has often resulted in hesitation before seeking medical advice.

Treatment

There is no established specific treatment for lichen sclerosus. When the disease is mild or asymptomatic no treatment is required. Cases with mild pruritis and soreness benefit from the application of bland emollient creams such as E45 (Crookes Products), which are soothing. Mild topical steroids in combination with antibacterial and antifungal compounds (for example, Daktacort, Janssen; Terra-Cortril, Pfizer) also appear to be of value in speeding resolution of exacerbations and preventing and treating bacterial or candidal superinfection. Lactulose is often useful in cases associated with pain on defaecation, and more potent laxatives such as senna may be required during exacerbations.

In severe cases, the use of potent topical steroid creams, for example 0·05% fluocinonide cream (Metosyn, Stuart), or 0·05% clobetasol propionate cream (Dermovate, Glaxo), is justified, applied twice daily for short periods of up to three weeks. The use of topical steroids in lichen sclerosus may be a source of concern, especially to non-dermatologists, in view of the risk of adding steroid induced atrophy to the atrophic scarring of the disease. In our experience, however, short courses of potent steroids produce considerable improvement. Furthermore, a recent study of seven adult cases treated with clobetasol propionate cream twice daily for 12 weeks showed histological improvement in all subjects (KL Dalziel, PR Millard, FT Wojnarowska, personal communication).

Prognosis

The prognosis is somewhat uncertain, but appears considerably better than in adults, as resolution may occur at or before puberty. Ditkowski *et al* recorded complete remission in six of eight reported cases by the age of 14.[15] Clark and Muller observed resolution, which was usually complete, in 12 of 24 cases of anogenital disease, but found no consistent temporal relation to the menarche.[11] Wallace reported complete resolution of symptoms in 20 of 35 girls with anogenital lichen sclerosus at or before puberty, although there were later recurrences of symptoms in three of these cases.[4] Tõrõk *et al* reviewed 33 girls with lichen sclerosus.[16] They reported complete disappearance of symptoms in a quarter of their cases, within one year of follow up, and a further half of their patients were improved at one and a half years. More recently, however, Ridley stated that she had never seen a case spontaneously resolve.[9] We have never observed complete resolution either, although many of our cases have improved to the point where they are asymptomatic. Extra-genital disease seems to carry the best prognosis.[4] [17] Complete resolution in adults is rare, and probably confined to extragenital lesions.[4] In adult lichen sclerosus carcinoma may supervene,[4] and although this complication has not been reported in childhood, Wallace recorded a case in whom carcinoma developed at the age of 30 in a patient who had suffered persistent lichen sclerosus since childhood.[4]

References

[1] Handfield-Jones SE, Hinde FRJ, Kennedy CTC. Lichen sclerosus et atrophicus in children misdiagnosed as sexual abuse. *Br Med J* 1987;**294**:1404–5.

[2] Priestley BL, Bleehan SS. Lichen sclerosus et atrophicus in children misdiagnosed as sexual abuse. (Letter.) *Br Med J* 1987;**295**:211.

[3] Davidson DC, Clarke MDB, Kean HB. Lichen sclerosus et atrophicus in children misdiagnosed as sexual abuse. (Letter.) *Br Med J* 1987;**295**:211.

[4] Wallace HJ. Lichen sclerosus et atrophicus. *Transactions of the St John's Hospital Dermatological Society* 1971;**57**:9–30.

[5] Harrington CI, Dunsmore IR. An investigation into the incidence of auto-immune disorders in patients with lichen sclerosus et atrophicus. *Br J Dermatol* 1981;**104**:563–6.

[6] Meyrick Thomas RH, Ridley CM, McGibbon DH, Black MM. Lichen sclerosus et atrophicus and autoimmunity—a study of 350 women. *Br J Dermatol* 1988;**118**:41–6.

[7] Shirer JA, Ray MC. Familial occurrence of lichen sclerosus et atrophicus. *Arch Dermatol* 1987;**123**:485–8.

[8] Meyrick Thomas RH, Kennedy CTC. The development of lichen sclerosus et atrophicus in monozygotic twin girls. *Br J Dermatol* 1986;**114**:377–9.

[9] Ridley CM. Lichen sclerosus et atrophicus. *Arch Dermatol* 1987;**123**:457–60.

[10] Chalmers RJG, Burton PA, Bennett RF, Goring CC, Smith PJB. Lichen sclerosus et atrophicus—a common and distinctive cause of phimosis in boys. *Arch Dermatol* 1984;**120**:1025–7.

[11] Clark JA, Muller SA. Lichen sclerosus et atrophicus in children—a report of 24 cases. *Arch Dermatol* 1967;**95**:476–82.

[12] Laude TA, Narayanaswamy G, Rajkumar S. Lichen sclerosus et atrophicus in an eleven year old girl. *Cutis* 1980;**26**:78–80.

[13] Pinkus H, Mehregan AH. *A guide to dermatohistopathology.* 2nd ed. New York: Appleton-Century-Crofts, 1976:364–6.

[14] Chernosky ME, Derbes VJ, Burks JW. Lichen sclerosus et atrophicus in children. *Arch Dermatol* 1957;**75**:647–52.

[15] Ditkowski SP, Falk AB, Baker N, Schaffner M. Lichen sclerosus et atrophicus in childhood. *Am J Dis Child* 1956;**9**:52–4.

[16] Tõrõk E, Őrley J, Gorácz G, Daróczy J. Lichen sclerosus et atrophicus in children. *Modern Problems in Paediatrics* 1975;**17**:262–71.

[17] Kindler T. Lichen sclerosus et atrophicus in young subjects. *Br J Dermatol* 1953;**65**:269–79.

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Archives of Disease in Childhood, 1989, **64**, 1207–1209

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Aetiology of severe pneumonia in developing countries

Sir,

Dr Ikeogu suggests, on the basis of his lung aspirate study of 40 children hospitalised in Bulawayo, that bacterial infection is not the commonest cause of severe pneumonia in children in Zimbabwe.[1] This contrasts with published data from at least 13 lung aspirate studies from developing countries showing the importance of bacterial infections, in hospitalised children with severe (predominantly lobar) pneumonia. While geographical differences undoubtedly exist there are remarkable similarities in the results from these studies. The statement that 'negative bacterial growth from lung aspirates implies acute viral infection in most cases' should be read with caution. Bullowa's study of 211 bacteraemic pneumococcal pneumonias has suggested that lung aspiration has a false negative rate of at least 22%.[2] Studies where viral cultures, immunofluorescence, or serology have been performed, together with lung aspiration or blood culture in children with severe pneumonia, have found evidence of viral infection only in approximately 30%. If a genuinely low bacterial isolation rate in Bulawayo is to be established convincingly, serum or urine should be tested for antibacterial activity, as history of recent antibiotic treatment can often be unreliable.[2]

Intervention trials from six countries have recently shown that improved case management with antibiotics may substantially reduce mortality from acute respiratory infections.[3] This strategy is not necessarily one of increasing antibiotic prescription and hence escalating costs. Although viral and bacterial pneumonias cannot be differentiated reliably by clinical or radiological findings, simple clinical signs can be used to distinguish lower from upper respiratory infections thus allowing antibiotic delivery to be directed to the former group and potentially reducing antibiotic use in the community.[4]

We are concerned that the low mortality in this series suggests that these patients may not be typical of the majority of children in Zimbabwe and that the epidemic nature of respiratory infections requires that the minimum study period be one year (invasive pneumococcal disease in The Gambia appears to be noticeably seasonal). Furthermore, although Dr Ikeogu emphasises supportive care methods, it should be recognised that these are not yet proved to be effective in reducing mortality from pneumonia in developing countries. The weight of currently available evidence supports early antibiotic treatment as the primary intervention for all severe pneumonia in developing countries.

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Dr Ikeogu comments:

Drs Campbell and Forgie raise a number of issues regarding my article on acute pneumonia.[1] Space does not allow me to discuss all the points raised. They express surprise about the low mortality in the patients in the series. In our unit a lot of emphasis is placed on supportive care even in those with bacterial pneumonia. The supportive care principles are based on simple pathophysiological considerations but mechanical ventilation is used very infrequently in our unit and none of the 40 children was ventilated. The argument here is not distinguishing upper from lower respiratory infection but determining the aetiology of acute lower respiratory infection and therefore deciding when to use antibiotics. I consider the use of the suggested simple physical signs[4] in arriving at this decision as an oversimplification, which is sometimes useful in situations where there are no doctors or paediatricians or facilities for appropriate investigations but which also, in my experience, often results in delayed referral to hospital often with disastrous consequences.

Also not treating upper respiratory infections because of absence of such simple signs as Drs Campbell and Forgie seem to suggest is dangerous in those areas with a high incidence of rheumatic fever. The difficulties in trying to simplify the management of respiratory infection in children are obvious and nothing can substitute experience backed up by appropriate investigations.

The purpose of my article was to indicate the possibility of regional differences in the patterns of pneumonia in developing countries and by so doing stimulate more investigations. Drs Campbell and Forgie agree with me that geographical differences and similarities do exist, a point reinforced by the absence of a single positive blood culture in any of the patients (this point was not mentioned in the article). The period of investigation included the peak period for respiratory infections and the population studied had no access to undocumented antibiotic exposure.

References

[1] Ikeogu MO. Acute pneumonia in Zimbabwe: bacterial isolates by lung aspiration. *Arch Dis Child* 1988;**63**:1266–7.

[2] Shann F. Etiology of severe pneumonia in children in developing countries. *Pediatr Infect Dis* 1986;**5**:247–52.

[3] World Health Organisation. *Case management of acute respiratory infections in children: intervention studies.* Geneva: WHO, 1988. (WHO/ARI/88.2.)

[4] Cherian T, Jacob John T, Simoes E, Steinhoff MC, John M. Evaluation of simple clinical signs for the diagnosis of acute lower respiratory infections. *Lancet* 1988;**ii**:125–8.

Seizures presenting as apnoea

Sir,

Investigations of the infant with a seizure disorder presented by Navelet *et al* do not provide adequate data to state that the recurrent episodes of intense cyanosis were due to seizure induced airway obstruction or a seizure induced prolonged absence of inspiratory efforts.[1] We accept that seizures may cause prolonged absence of breathing effort and hypoxaemia and have previously described one patient with this problem.[2] In our patient, however, the apnoea was present for more than 50 seconds before severe hypoxaemia became apparent. In situations of complete airway obstruction due to imposed apnoea the onset of sufficient hypoxaemia to produce cyanosis does not appear until after 60 seconds of absent airflow.[3] In our opinion, it is more likely that the primary cause of the sudden onset and rapid progression of hypoxaemia was intrapulmonary shunting and prolonged expiratory apnoea.[4] This may have triggered the seizure shown in the recording or may have resulted from the seizure. In order to answer this, it would be required to document the temporal association between the onset of hypoxaemia and development of seizure activity.

The onset of cyanotic episodes with meals or pain, the lack of response to antacids, metoclopramide, atropine, and phenobarbitone and the early onset and intensity of cyanosis would be typical of a sudden intrapulmonary shunt and prolonged expiratory apnoea.[4] These latter episodes are induced in infants under 6 months typically by feeding or painful or stressful stimuli, and the resulting seizure is secondary to the hypoxaemia.

It is also possible that cerebral injury resulting from severe hypoxaemia early in life may have produced a focus for the subsequent development of epilepsy.

We suggest that all polygraphic monitoring during cyanotic episodes should include measurements of oxygenation, most reliably sensed by a pulse oximeter in a beat-to-beat mode.

References

[1] Navelet Y, Wood C, Robieux I, Tardieu M. Seizures presenting as apnoea. *Arch Dis Child* 1989;**64**:357–9.

[2] Southall DP, Stebbens V, Abraham N, Abraham L. Prolonged apnoea with severe arterial hypoxaemia resulting from complex partial seizures. *Dev Med Child Neurol* 1987;**29**:784–9.

[3] Southall DP, Stebbens VA, Rees SV, Lang MH, Warner JO, Shinebourne EA. Apnoeic episodes induced by smothering—two cases identified by covert video surveillance. *Br Med J* 1987;**294**:1637–41.

[4] Southall DP, Talbert DG, Johnson P, *et al.* Prolonged expiratory apnoea—a disorder resulting in episodes of severe arterial hypoxaemia in infants and young children. *Lancet* 1985;**ii**:571–7.

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Range of neural tube defects in southern India

Sir,

The article on neural tube defects in southern India by Kulkarni *et al* mentions 'widespread prenatal screening and termination of affected pregnancies' as contributing towards the downward trend of these defects in Western countries including the United States and Scotland.[1] However, the Report of the Chief Medical Officer for England and Wales in 1985 states that 'screening and subsequent elective abortion has not been a major cause of the decline'.[2] A similar decline has occurred in the Republic of Ireland, where abortion is not carried out.[3]

References

[1] Kulkarni ML, Mathew MA, Reddy V. The range of neural tube defects in southern India. *Arch Dis Child* 1989;**64**:201–4.

[2] Chief Medical Officer. *Annual report 1985*. London: DHSS, 1985.

[3] Radic A, Dolk H, de Wals P. Declining rate of neural tube defects in three eastern counties of Ireland: 1979–1984. *Ir Med J* 1987;**80**:226–8.

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Breath hydrogen excretion in infants with colic

Sir,

In some babies with troublesome crying the features of intense sympathetic activity after a prolonged screaming episode of, say, 30 minutes are very striking. These babies have a pronounced tachycardia, sweat, and become red in the face. Is it possible that the work of crying results in a shortened intestinal transit time with increased delivery of lactose to the colon reflected in high breath hydrogen excretion as Miller and colleagues have demonstrated?[1] Another observation is that babies with troublesome crying very often stop crying after hospital admission, often within 24–48 hours, with no alteration to their diet.[2] It would be very interesting to know if the hydrogen breath excretion dropped over this same short period. This may help to distinguish whether the abnormal results of Miller *et al* reflect a primary gut abnormality or a secondary phenomenon. A study to examine this may be easier to design than one to examine the effect of altering the lactose content of the diet.

References

[1] Miller JJ, McVeagh P, Fleet GH, Petocz P, Brand JC. Breath hydrogen excretion in infants. *Arch Dis Child* 1989;**64**:725–9.

[2] Barbero GJ, Rigler D, Rose JA. Infantile gastrointestinal disturbances: a pilot study and design for research. *Am J Dis Child* 1957;**94**:532.

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Perinatal lessons from the past

Sir,

May I correct one reference in Dr Dunn's excellent reminder that we often rediscover past knowledge because we forget to review the literature of our predecessors?[1] The biblical text quoted at the beginning of the article is from *Ecclesiastes* (the book following *Proverbs*), and the preceding verse (9) ends '. . . what has been done will be done again, and there is nothing new under the sun.' The book called *Ecclesiasticus* (found in the *Apocrypha*) forms another part of the ancient 'wisdom literature', and hints that the doctor and academic may have suffered financial restraints and 'university' squeezes in ancient times too. Chapter 38 verse 1 reminds the reader to . . . 'Honour the doctor for his services' . . . and verse 24 of the same chapter states: 'A scholar's wisdom comes from ample leisure; if a man is to be wise he must be relieved of other tasks'.

Yes, there is nothing new under the sun!

Reference

[1] Dunn PM. Perinatal lessons from the past. *Arch Dis Child* 1989;**64**:493.

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Autosomal recessive hypophosphataemia

Sir,

In 1976 we described for the first time autosomal recessive hypophosphataemia.[1] Family testimony and obstetric records leave no doubt as to the identity of the (now deceased) mother of the two affected offspring of the first cousin marriage we reported. The evidence for paternity we cited in our paper was, however, based only upon blood group analysis. In order to confirm paternity beyond doubt, we have re-examined the question using HLA and DR typing and genetic fingerprinting.

HLA and DR typing show the putative father to share one haplotype with the two affected offspring, antigens A11, BW50, and DR7 being common to all three individuals. Genetic fingerprinting (Cellmark Diagnostics) shows the father and his affected son to share 24 bands (42 bands identified in the father and 38 in the son). The father and affected daughter share 29 bands (42 bands identified in each). Calculation indicates that the likelihood of stated over random paternity is 2×10^6 and 8×10^9 in the case of the son and daughter, respectively. Relative probability of the putative father being the true parent rather than an uncle of the two is respectively 17 and 339. We are satisfied, therefore, that autosomal recessive transmission occurred in the family we described.

The existence of several mendelian forms of hypophosphataemia provides strong evidence for the heterogeneity of renal phosphate transport systems. Our confirmation that autosomal recessive transmission truly occurred in the family we described strengthens the case that such heterogeneity exists.

Reference

[1] Stamp TCB, Baker LRI. Recessive hypophosphataemic rickets and possible aetiology of the vitamin D-resistant syndrome. *Arch Dis Child* 1976;**51**:360–5.

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British Paediatric Association

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Abstracts for plenary spoken sessions

Street kids: sex and sexually transmitted diseases (STD): what they know and do. NE MacDonald, WW Bowie, JA Doherty, and J Radford (Ottawa, Canada).

'Street kids' (SK=youths who spend most of their time on city streets) are at high risk for STD. To determine what SK in Canada know and do about sex and STD, 656 SK from 10 cities were interviewed for 30–45 min each. SK were recruited directly from the street or through social service agencies. 90% approached participated. The M:F ratio was 1·1:1, age range 15–20 (mean 17·4) and their primary tie to the street was prostitution (14%), drug/alcohol abuse (13%), crime (19%), homelessness (39%), and unemployment (16%). Of the 94% who were sexually active, 22% started before 12 years, 12% before 9 years. Two thirds had >5 lifetime sexual partners: mean 21 (excluding prostitutes, mean=200). Of the males, 30% had had sex with other males but only 2% said they were homosexual and 4% bisexual. Overall, 21% SK had engaged in anal sex, 4% often. Less than 20% SK regularly used condoms. Although only 7% worried about contracting an STD, 20% had already had one. Most obtained therapy (94%) and completed it but only 25% went for follow up. SK know more about AIDS than other STD and were more informed than age-matched urban controls. STD knowledge came from school and peers who had had STD. SK preferred STD data from doctors or clinics not peers or parents because of concerns about accuracy and confidentiality. Interviewers judged SK sexual behaviour to be 'normal' and adapted for survival on the street and STD unimportant to them. Thus if STD are to decrease in SK, improved social as well as medical/educational interventions are needed.

Perianal appearances in childhood constipation. U Agnarsson, C Gordon, C Wright, G McCarthy, and N Evans (Brighton).

With regard to the debate on anal appearances in sexually abused children and in children with constipation we assessed the appearance of the perianal area in 102 consecutive children, 55 boys and 47 girls aged 6 weeks to 13 years, presenting to this hospital with mild to moderate constipation and/or soiling. All except two were primary GP referrals and coexistent sexual abuse could not be excluded, although no evidence came to light after detailed history. Note was made of the presence and nature of anal dilatation (ad), whether full (relaxation of both anal sphincters) or partial (external sphincter relaxation only) and whether seen immediately, at 30 or 60 seconds or on stretching of the buttocks. Faecal loading was assessed simultaneously. The number of anal fissures (af) whether fresh or old, anal tags, anal scars and perianal veins were charted, the latter graded as not seen, visible, prominent and varicose. The presence and nature of perianal erythema and blueness (graded 0–3) was noted. Results: 22 children had ad (21%), nine full (8·7%) and 13 partial (12%). Rectal or abdominal loading was found in seven of the nine children with full and in six of the 13 children with partial ad. The two children with no faecal loading and full ad were normal on subsequent follow up. In 25 patients (24·5%) af were seen and 15 of these were in children less than 18 months old. Eight children had af and ad. Anal tags and anal scars were seen in one patient respectively. Sixty six patients had some perianal erythema and 45 had some perianal blueness. Perianal veins were seen in 22 patients. In 21 patients they were just visible and prominent in only one. Conclusions: full anal dilatation without evidence of faecal loading is found in 1–2% of mildly constipated children. Minor anal fissures are very commonly found in such children.

The sexually abused battered child. CJ Hobbs and JM Wynne (Leeds).

Since beginning of 1985 we have seen 122 children (72 girls, mean age 5·6 years and 50 boys, mean age 6·8 years) with both non-accidental injury and sexual abuse. 69 presented with non-accidental injury, 36 with suspected sexual abuse and 17 with general concern. 57 were under 5 years (47%) and 103 under 10 (84%).

Six children sustained fractures, 105 had excessive or unusual bruising, 20 suspicious burns or scalds, and 38 scratches or lacerations. Frequent sites for bruises were thighs (68 children), buttocks (37), back (35), face and head (35), upper arms (33), knees (30), abdomen (19), and paragenital (7). Grip marks on knees, thighs and arms were common.

One hundred and two children suffered penetration of mouth, anus, or vagina. Despite physical violence, 39 made full and 26 partial disclosure of sexual abuse. Four children died.

Doctors who see physically abused children are used to looking for signs of neglect and failure to thrive. This study indicates the importance of considering sexual abuse in the non-accidentally injured child.

Consistent clustering of child abuse in an inner city borough from 1982–1988. AM Cotterill, S Jenkins, and CBS Wood (London).

The geographic mapping of registered child abuse cases reveals clusters of cases in small areas, usually housing estates, which contain 70% of cases registered.[1] The prediction of future clusters is best and most simply done by mapping rather than using census derived information.[1] This study extends the study period from 1985 to September 1988 and investigates the recent changes in distribution, and examines the effects of the increase in sexual abuse registration. The households containing at least one child on the child abuse register were marked on a large scale map and note was made of the date of registration and the type of abuse. Maps were made for all abuse for 1982–1988, 1982–1985, 1985–1988, and for sexual abuse for 1985–1988. The overall rate of abuse registration declined from 4·7 (1984–1985) (households with at least one child on the child abuse register per 1000 households with children under the age of 16 years) to 3·8 (1985–1986), 3·4 (1986–1987), and 2·7 (1987–1988), while the rate of sexual abuse registrations increased from 0·4 (1985/86), 0·8 (1986/87) to 1·0 (1987/88), with also a relative increase from 10% to 37% on all registrations. In comparison with the map for 1982/85, the map for 1985/88 shows a very similar clustering of cases with 67% lying in clearly identifiable clusters. Twelve clusters could have been predicted from the 1982/85 map and these predicted clusters contained 57% of all cases and 56% of sexual abuse cases registered in 1985/88.

This study shows over a seven year period a consistent clustering of child abuse registration within certain housing areas, which contain 70% of all registered cases of abuse. The increase in sexual abuse registration did not alter the clustering phenomenon. These findings may lead to a change in the methods of primary prevention of child abuse to local community schemes within the identified cluster areas.

Reference

[1] Cotterill AM. *Child Abuse Negl* 1988;**12**:461.

Child sexual abuse video—is seeing believing? E Vizard, M Wiseman, A Bentovim, and J Leventhal (London and Yale).

Aims: (a) to assess reliability of a semi-structured interview with suspected sexually abused children. (b) To assess whether blind-raters of videotaped material, make correct judgments re CSA? (c) What are the differing professional perceptions of videoed interviews? (d) Hypothesis generation.

Method: 28 raters from psychiatry, psychology, social work, the law and the police force, were asked to rate 12 edited videotapes of children who may have been sexually abused. Raters were asked to say whether children had been sexually abused and why they held this opinion. Ratings were compared with file data, to establish validity.

Results: (a) good agreement between blind videotape raters and file data rating, on the likelihood of sexual abuse. (b) Police noted subtle nonverbal child indicators of CSA, but lawyers were impressed by articulate children.

Conclusion: That semi-structured interview seems to be diagnostically valid, and of evidential value. The legal profession put the onus on the child to be convincing, whereas police officers try to understand child behaviours.

The Northumbria women's police doctor scheme: a novel approach to the forensic examination in child sexual abuse. CM Wright, L Duke, E Fraser, and L Sviland (Newcastle upon Tyne).

As more children present to the police with disclosed sexual abuse, problems may arise in obtaining a medical opinion. Paediatricians, though experienced in other forms of abuse, often lack the forensic skills required by the police.

In 1983 Northumbria police recruited a number of women doctors to examine all victims of sexual assault, without undertaking other police surgeon duties. In 1986 the doctors on the scheme, drawn mainly from general practice and paediatrics, examined 312 victims. 82% of victims were under 16 and 27% under 6 years; child sexual abuse thus constitutes most of the work load. The majority of the children presented with a disclosure by the child or following parental suspicion. 51% assailants were related to the victims, 32% being fathers or stepfathers; only 6% were strangers. Physical signs were found in more than half of those examined.

The doctors work closely with five police child abuse units whose women officers conduct all the interviews. A variable degree of liaison has been achieved with local paediatricians and psychiatrists for providing aftercare. The scheme provides a forum for education and support and has collectively gained much expertise. Similar schemes could be set up elsewhere in the country, allowing paediatricians to learn forensic skills and thus provide a valuable service to police, social services, and to children.

Host defence mechanisms. IM Roitt (London).

Antibodies in collaboration with complement and polymorphonuclear leukocytes constitute a triad of systems which are effective against extracellular organisms, constituting so called 'humoral immunity'. Cell mediated immunity, involving the T-lymphocyte, is essentially directed to eradicating intracellular parasites. The T-cell antigen-specific receptor recognises a combination of a major histocompatibility complex (MHC) molecule, together with a peptide fragment. The MHC molecule tells the T-cell which type of cellular target that it is encountering, while the components of the intracellular parasites are broken down to peptide fragments which reach the surface in association with the MHC molecule and are indicators of their intracellular parasitic origin.

References

1 Roitt IM. *Essential immunology*. 6th ed. Chapters 1 and 2, and sections on T-cell receptor, MHC and T-cell recognition of antigen in chapters 3 and 4. Oxford: Blackwell Scientific Publications.

2 Male D, Champion B, Cooke A. *Advanced immunology*. Chapters 3, 5, 6, and 7. JB Lippincott, 1987.

3 Kindt TJ, Long EO, eds. *Current opinion in immunology*. London: Current Science, 1988;1:98–111.

Neutrophil-endothelial adhesion responses. KD Forsyth and RJ Levinsky (London).

In inflammatory states neutrophil migration from the vascular to the extravascular compartment is increased. The mechanisms of this enhanced response is due to alterations of the neutrophil and endothelial surface. For instance, neutrophil stimulants increase adhesion to endothelium and endothelial stimulants such as IL1 increase neutrophil adherence. Neutrophil binding to endothelium is mediated (at least in part) by the Leu-cam's (leucocyte adhesion molecules) LFA–1, CR3 and p150,95 (CD18, CD11a, b, and c). Baseline neutrophil adherence to endothelium can be inhibited partially by LFA–1 antibody (CD18 and 11a). Stimulation of neutrophils with inflammatory stimulants increases neutrophil adherence by LFA–1 and other as yet unrecognised mechanisms. Interleukin 1 also increases adhesion by new synthesis of the LFA–1 ligand on endothelium. Furthermore, the LFA–1 molecule on neutrophils can be increased antigenically and functionally by incubation of neutrophils with anti-neutrophil (CD15) antibodies, which bind to an oligosaccharide (LNF III) present on the LFA–1 chains, probably inducing a conformational change in the receptor. LNF III is present on other cell types, but is 'masked' by sialic acid. If there is an in vivo ligand for LNF III or if desialation occurs, that is, by neuraminidases from bacteria, increased neutrophil adhesion to endothelium may occur and contribute to the inflammatory response. Understanding of adhesion mechanisms of inflammatory cells to endothelium offers potential for therapeutic intervention in cases where host defence mechanisms are self-damaging. We have explored the use of an anti CD18 antibody in a condition of endothelial damage, the haemolytic ureamia syndrome (HUS). In HUS, there is a 1·5 to 2 times increase in neutrophil binding to endothelium and endothelial damage. The CD18 antibody is able to inhibit endothelial damage in certain cases.

T cell-mediated changes in epithelial cell proliferation and goblet cell numbers in human fetal colon: a model of colitis. CM Evans, JA Walker-Smith, and TT MacDonald (London).

Immune mechanisms important in the pathogenesis of colonic inflammation are not well understood. An organ culture model was therefore used to study the effects of T cell activation in the human colon.

Lamina propria T cells in explant cultures of human fetal colon (16–20 weeks' gestation) were activated in situ with pokeweed mitogen or anti-CD3 antibody, and compared with unstimulated controls.

After three days of culture, T cell stimulated colonic explants showed a 2–4 fold increase in crypt epithelial cell proliferation and a decrease in crypt goblet cells of up to 20 fold (n=15 experiments). After five days, there was flattening of the surface epithelium with severe loss of goblet cells in T cell stimulated explants, and by day 7, severe and extensive epithelial damage had occurred. A slight fall in goblet cell numbers without crypt hyperplasia was observed in control cultures by day 7, but the rate and intensity of depletion were less than in stimulated explants, and the epithelium remained intact.

Goblet cell depletion, crypt hyperplasia, and epithelial cell damage are common histological findings in colonic disease (particularly ulcerative colitis). These experiments suggest that T cells may have an important role in the pathogenesis of colitis. The model provides a new system by which the mechanisms of T cell-mediated damage in the human colon can be studied.

Kawasaki disease—anti endothelial cell and antineutrophil cytosolic antibodies—a new approach to diagnosis with possible pathogenetic implications. EJ Tizard, E Baguley, V Shah, GRV Hughes, and MJ Dillon (London).

There is increasing evidence that immunological mechanisms play a role in the pathogenesis of Kawasaki disease (KD).

Cytotoxic antiendothelial cell antibodies (AECA) causing lysis of cytokine stimulated cells have previously been reported (*J Exp Med*, 1986). We have used a cellular based ELISA assay to demonstrate the presence of antibodies directed against both cytokine stimulated and unstimulated endothelial cells. Sera from 32 patients with KD were evaluated; 21/32 patients had detectable AECA (mainly of the IgM class but some IgG). This compared with 0/27 IgM and 0/12 IgG in normal controls.

Cytokine stimulation resulted in upregulation in 5/18 patients. Serial measurements showed an initial rise in IgM titre with a fall in the convalescent period.

Antineutrophil cytosolic antibodies (ANCA) have been found in certain forms of adult vasculitis (Wegener's granulomatosis and microscopic polyarteritis). We have developed an ELISA assay to assess the presence of ANCA in KD and found that 20/28 patients had raised titres.

Of the patients in whom both AECA and ANCA were measured only 12/26 had both antibodies suggesting that these are directed against different antigens.

We suggest that these antibodies may be useful markers of disease activity but they may also have important pathogenetic implications for this and other forms of vasculitis.

Liver membrane-specific T cell clones in autoimmune chronic active hepatitis (aCAH). L Wen, A Lobo-Yeo, M Peakman, AP Mowat, G Mieli-Vergani, and D Vergani (London).

Patients with aCAH have increased numbers of activated circulating T-lymphocytes expressing interleukin 2 receptors (IL–2R). By sequentially incubating peripheral blood mononuclear cells (PBMC) of a patient with aCAH with recombinant IL–2 and PHA at a concentration of 0·3 cells/well, 11 T-cell clones were generated, 10 of which were CD4+ and one CD8+. Two CD4+ clones proliferated in response to rabbit liver membrane homogenate (RLM) when co-cultured with irradiated autologous PBMC as antigen presenting cells, but not with allogeneic PBMC. No proliferation was observed when rabbit kidney membrane was used as stimulating antigen. Proliferation of RLM-specific T cell clones was blocked by adding anti-CD4, anti-HLA DR and anti-IL2R, the inhibition being reversed in the latter case with excess IL–2. Six T cell clones (4 CD8+, 2 CD4+) generated from a control under similar conditions were unresponsive to RLM whether presented by autologous or allogeneic PBMC. These results show that T cell clones can be generated from circulating IL–2R+ T cells of patients with aCAH. Their specificity for liver cell membrane, the likely target of the immune attack in aCAH, indicates their involvement in the pathogenesis of this disease.

How HIV attacks the immune system. RA Weiss (London).

The human immunodeficiency viruses (HIV–1, HIV–2) cause acquired immune deficiency syndrome (AIDS). These viruses gain entry into T-helper lymphocytes by subverting the CD4 cell surface antigen as a high affinity receptor recognised by a site on the outer coat protein (gp120) of the virus. Full replication of the virus inside the cell causes cell death leading to eventual depletion of circulating T-helper cells and immunodeficiency. The CD4/gp120 interaction can be cytopathic by other mechanisms too. HIV also infects monocytes, macrophages, and in culture, muscle, gut and brain glial cells. Whether CD4 acts as the HIV receptor for these cell types is not so clear. The infection of other cell types helps to explain the wasting disease and neuropathy seen in HIV infected subjects, not least in paediatric AIDS. The binding of gp120 to CD4 can be blocked by a variety of antibodies and recombinant CD4 decoy proteins, which are being explored as potential means of therapy.

References

[1] Pinching AJ, Weiss RA, Miller D. AIDS and HIV infection: the wider perspective. *Br Med Bull* 1988;**44:**1–234.

[2] Weber JN, Weiss RA. HIV infection: the cellular picture. *Sci Am* 1988;**256:**100–9.

Paediatric AIDS and HIV infection in the United Kingdom. A Ellam and N Gill (Colindale).

The British Paediatric Surveillance Unit reporting scheme is an integral part of the national surveillance of paediatric AIDS. As of September 1988, 30 cases of AIDS in children aged 14 years and under had been reported to the surveillance centre at CDSC, 25 through the BPSU. Of these six were haemophiliacs, five had received blood transfusions, and the remaining 19 (63%) were born to infected mothers.

In the same period, 276 laboratory reports of HIV antibody children were received. A total of 159 were in haemophiliacs, nine in blood recipients, and 101 (37%) born to infected/at risk mothers.

An analysis of data from the two systems will be presented, detailing risk factors, sex, age at onset of symptoms, the clinical presentation, and the survival in those who subsequently developed AIDS.

The changing pattern of risk factors over time shows an important increase in the role of injecting drug use, either in the mother or her partner, and an increase in heterosexual contact generally.

Data up to the end of March 1988 will be included.

Cloning of a Chlamydia trachomatis DNA fragment endowing recombinant Escherichia coli with adherent properties for eukaryotic cells. I Allan and ER Moxon (Oxford).

Chlamydia trachomatis is a major cause of sexually transmitted and ocular disease, and, as such poses a considerable threat to the neonate and young child.

The obligately intracellular lifestyle of this bacterium presents many practical problems to its study; however, it may also provide unique potential targets for intervention and immunoprophylaxis. The initial intraction between the parasite and its host cell may well represent just such a vulnerable step in the developmental cycle of the pathogen. In order to study components which may be involved in this initial interaction we have constructed a genomic library of *C trachomatis* by digestion of chlamydial DNA with the restriction endonucleases Pst I and Xba I and ligation of the DNA fragments into the plasmid pUC–19. These recombinant plasmids were then introduced into *E coli* and the resulting recombinant bacteria screened for enhanced association with eukaryotic cell monolayers, by comparison with non-recombinant *E coli,* in an adherence assay. One clone of recombinant bacteria resulting from this procedure exhibited markedly enhanced association with eukaryotic cells.

Sequencing of the chlamydial DNA in this recombinant has revealed the potential to code for a polypeptide of 88 amino acid residues with two striking structural features. Firstly, the central portion of the polypeptide is highly hydrophobic—resembling the membrane spanning domains of known outer membrane proteins of bacteria. Secondly, the carboxy-terminal region of the polypeptide is highly positively charged, and it is tempting to speculate that this region may play a critical role in the initial interaction of the parasite with negatively charged components of the host cell surface.

Specific maternal antibody levels and their isotypes in group B streptococcal sepsis in the newborn period. RG Feldman and A Ferrante (London and Adelaide).

It is recognised that a major risk factor for the development of group B streptococcal (GBS) sepsis in the newborn period is low or absent maternal levels of specific IgG antibody. Enzyme immunoassays were developed to measure absolute quantities of anti-GBS type III polysaccharide antibodies and their subclasses.

Sera were examined from 18 healthy non-pregnant controls and nine mothers of infants with proven GBS type III septicaemia (none of the mothers themselves were infected). Eight (47%) of the controls had protective anti-GBS type III IgG levels (≥2 μg/ml), while only one of the mothers of the infected infants had a protective antibody level (2·6 μg/ml). The mean anti-GBS type III antibody level of the control group was 6·35 μg/ml (range 0 to 59·2 μg/ml) and that of the mothers of infected infants 0·7 μg/ml (range 0 to 2·6 μg/ml). The finding in this preliminary study that the mothers of infected infants had low levels of anticapsular antibody is in agreement with previously published data. The proportion of healthy controls in this study (47%) who have protective levels of antibody is higher than reported in the USA population (0 to 28%) and this may explain the observed difference in incidence of infection between the two countries (0·3/1000 live births in the UK versus 0·7 to 20·2/1000 in the USA).

With respect to the IgG subclasses, every serum tested including the controls contained GBS type III specific IgG_2 and three sera (2 controls and one mother of an infected infant) contained, in addition, detectable specific IgG_1. No IgG_3 was detected in any of the sera. One serum which was not drawn from this study contained a hyperimmune level of anti-GBS type III antibody (1200 μg/ml) and contained >99% IgG_2 but also detectable quantities of IgG_4. No other serum contained anti-GBS type III specific IgG_4. These findings suggest that GBS type III specific IgG_4. These findings suggest that GBS type III carbohydrate elicits a similar humoral response to that seen in many other bacterial carbohydrates such as *Haemophilus influenzae* serotype b.

Human milk inhibits adhesion of enteropathogenic Escherichia coli (EPEC) to human epithelial cells. KA Nathavitharana, S Knutton, D Catty, and AS McNeish (Birmingham).

Adhesion of EPEC to the intestinal mucosa is known to be an important event in colonisation and the development of diarrhoeal disease. Human milk is thought to possess anti-adhesive factors. The object of this study was to assess the presence or absence of anti-EPEC adhesive factors in human milk using an in vitro human epithelial cell (HEp–2) adhesion assay. The adhesion index was defined as the percentage of cells with adherent microcolonies (>5 bacteria) of EPEC. The classical 0111 serogroup EPEC strain used for this study produced a mean adhesion index of 37 (range 30–42). Twenty five of 39 human milk specimens tested produced a marked reduction in the adhesion index to 2 (range 0–8). 12 of 13 specimens with demonstrable 0111-specific secretory IgA (sIgA) produced a marked reduction in the adhesion index to 1 (range 0–8) whereas 13 of 26 specimens without demonstrable 0111-specific sIgA also produced a marked reduction of the adhesion index to 2 (range 0–8). Absorption of the 0111–specific sIgA from 4 milk specimens did not affect the adhesion index. These results confirm the presence in some specimens of human milk of anti-EPEC adhesive factors, presumably in milk from those women exposed to EPEC bacteria. Such anti-adhesive factors appear to be unrelated to EPEC O-antigen specific sIgA antibody in milk.

Twenty years experience of renal transplantation in children. SPA Rigden, GM Ward, C Turner, M Bewick, G Koffman, GB Haycock, and C Chantler (London).

In the 20 years since November 1968, 249 children (159 male, 90 female; age range 9 months–18 years) have received 325 renal allografts. Fifty four children have been retransplanted once and 11, twice. Eighty grafts were from live related donors. In the first quartile, 75% of the children were >10 years of age at transplantation and the youngest child 7 years; in the fourth quartile 17% of the children were <5 years and 29% aged 5–10 years at transplantation. Primary renal diseases were congenital abnormalities, including reflux nephropathy in 46%, inherited diseases in 25%, and glomerulonephritis 14%.

Actuarial survival (AS) for children transplanted between 20 November 1968 and 31 December 1987 is 79% at 14 years and for those transplanted since 1 October 1983 is 94% at 4 years. AS for the 38 children aged < than 5 years at transplantation is 79% at 5 years. AS for all first grafts (live related and cadaver) is 62% at 14 years and for first grafts performed since 1 October 1983 is 68% at 4 years. AS for first grafts in children aged < than 5 years is 67% at 5 years.

Seventy of the surviving children are now more than 18 years old; 41 of them have a functioning first graft, 22 have been retransplanted, and six have returned to haemodialysis. Thirty five are in employment and 13 pursuing further education. Twelve are known to be unemployed. Eight of these young adults are married and two have children.

Familial adenomatous polyposis coli is now a paediatric problem. FI Lalloo, J Burn, PD Chapman, CM Wood, EJ Eastham, JDA Delhanty, MJ Rhodes, and A Gunn (Newcastle upon Tyne, London, and Ashington).

Familial adenomatous polyposis coli (FAPC) is an autosomal dominant disorder, characterised by multiple adenomata of the large bowel with a propensity to early malignant change. Co-existent cutaneous and/or skeletal involvement attracts the eponym Gardner's syndrome. We have ascertained 38 families containing 60 affected individuals and 206 first or second degree relatives. These data derive from the Northern Regional Polyposis Registry, a collaborative screening programme involving 72 surgeons, which has in its first two years increased from 21 to 176, the number of relatives being screened.

The recent localisation of a gene for FAPC to chromosome 5q raises the possibility of early carrier detection on the basis of linkage to polymorphic DNA markers. In addition, we have found that multiple area of congenital hypertrophy of the retinal pigment epithelium identify 94% of obligate gene carriers (Chapman PD *et al*, in press). Traditionally, individuals at risk have annual bowel examination from puberty. Appearance of polyps under 14 years has been reported, however, including children as young as 6 years presenting with carcinoma. On the basis of the 70 children at risk we will discuss the feasibility and desirability of early carrier detection using a combination of eye and DNA examination. The optimal choice of screening procedure and age at commencement can then be considered.

Improving prognosis for osteosarcoma—preliminary results of a European study. AW Craft (Newcastle upon Tyne).

The prognosis for patients with osteosarcoma treated by amputation alone is only 20%. The addition of chemotherapy in the 1970s led to a suggestion of striking improvements in survival and two randomised studies with a no chemotherapy arm have shown a clear benefit with chemotherapy. The optimum regime remains to be determined. In 1983 the European Osteosarcoma Intergroup was established representing the United Kingdom Children's Cancer Study Group, Medical Research Council International Paediatric Oncology Society, and the European Organisation for the Research and Treatment of Cancer. A study was designed to compare the effectiveness of two regimes, each utilising the same two drugs—that is, adriamycin and cisplatinum, with one arm containing in addition methotrexate (arm 2). A total of 297 patients were entered between 1983 and 1986. Forty four had metastases at the time of diagnosis and 23 had an amputation before chemotherapy. There was excess of liver toxicity in arm 2 and neurotoxicity in arm 1. Definitive surgery of the tumour was undertaken at week 9 in both arms. Seventy six had an amputation and 120 had conservative surgery with either insertion of a metal prosthesis or a tibial rotationplasty. Survival at 4½ years in arm 1 was 65% and arm 2, 33% (p=0·037) and disease free survival 57% and 38% (p=0·009). For those patients with metastases at presentation survival was better in arm 2—that is, 61% *v* 10% (p=0·009) at 42 months. These survival figures are comparable with the best current multi-institutional studies most utilising prolonged and more complex chemotherapy. A second EOI study is now in progress comparing arm 1 of the first study with a multidrug regime based on the best published results by Rosen.

This study demonstrates the benefit to be achieved by centralisation of care for patients with osteosarcoma and the increasing use of conservative surgery admirably demonstrates the changing philosophy in paediatric oncology from 'cure at any cost' to 'cure at least cost'.

Intellectual impairment in 4 year olds with early treated phenylketonuria: relationship to dietary control. I Smith, MR Beasley, and AE Ades (London).

In early treated children with PKU who were born in the UK between 1964 and 1980, intelligence quotients (IQs) measured at 4 years of age using the Stanford Binet have been re-examined to take account of the rising IQ in the general population. In children born between 1964 and 1971 (cohort I) IQs rose from approximately −1·5 SD (−22·5 IQ points) to −0·7 SD (−10 IQ points). Children born between 1972 and 1980 (cohort II) showed no further rise. The proportions of children likely to require special education were 16% and 8% for cohorts I and II respectively. After allowing for social class, lower IQ was significantly and independently associated with later age at the start of treatment, higher phenylalanine concentrations at diagnosis and, during treatment over the first four years, higher average phenylalanine concentrations and prolonged periods of low phenylalanine concentrations. In both cohorts children with a mean phenylalanine concentration during treatment of over 700 μmol/l had mean IQs 1 SD (16 IQ points) below the means in children with a mean phenylalanine of 300 μmol/l; the relationship between IQ and phenylalanine control was approximately linear. Forty six children in cohort II who received the 'best' treatment (on diet by 20 days of age, average phenylalanine concentrations below 400 μmol/l, but not below 120 μmol/l for more than 2 months) had a mean IQ, after adjustment for social class, of 112·6 and very close to the estimated population norm for the Stanford Binet of 112·4.

We conclude that, unless blood phenylalanine concentrations have been below 400 μmol/l for most of the first four years of life, children with phenylketonuria are likely to suffer some degree of intellectual impairment.

Not so sudden infant death. R Meadow (Leeds).

Some children registered as dying from sudden infant death syndrome (SIDS), or who are thought to have recurrent apnoea, have been suffocated.

Twenty one young children who had been suffocated were studied. The certainty, or near certainty, of suffocation was based on maternal confession, reliable observation of the suffocation, or successful prosecution in a criminal court.

The children came from 21 different families. They had 10 live siblings and 15 who had died suddenly and unexpectedly in early life. The median age of death, or of discovery of suffocation, was 7 months; the median age of siblings, death was 6 months. Twenty of the 21 suffocated children had had recurrent apnoea, cyanosis, seizure, or near miss cot death; at least 11 of the dead siblings had similar episodes. Nine of the suffocated children had had other unexplained disorders including bleeding.

The characteristics of the 21 suffocated children differ from those of SIDS:

	Suffocation (%)	*SIDS (%)*
Previous apnoea	90	<10
Other unexplained disorder	40	<5
Age over 6 months	50	<15
Dead sibling	50	2

These differences should allow some cases of suffocation to be detected earlier and for intervention before brain damage or death occurs.

Single dose vitamin E prophylaxis for intraventricular haemorrhage (IVH). ML Chiswick, G Gladman, S Sinha, J Davies, and DG Sims (Manchester).

A randomised controlled trial from this centre showed that three daily doses of IM vitamin E protected against IVH in babies <33 weeks' gestation and that early supplementation was important. We were concerned about the problem of daily IM injections in babies who had little muscle bulk, and following the trial we instead gave all babies <33 weeks a single IM injection of vitamin E (20 mg/kg) soon after birth (median 2h, inborn), or on admission to the unit (median 12h, outborn) without changing our management policy in other respects. Risk factors for IVH were prospectively noted as in our previous trial, and babies received frequent ultrasound brain scans. Among all babies who received single dose prophylaxis (n=121) the incidence of IVH was significantly lower than in the original control population (13·2% *v* 34·3%; 95% CI for difference 10·3–31·9%).

A protective effect against IVH was still observed when inborn babies were considered separately (95% CI for difference 12·7%–36·8%), in spite of them having a significantly higher frequency of risk factors for IVH compared with the original inborn controls. In contrast, among referred babies who received single dose prophylaxis (median time 12h), the incidence of IVH (21·2%) was lower than the original referred controls (32·0%) but not significantly so. These results support the notion that single dose IM vitamin E gives better protection against IVH if given soon after birth and should stimulate exploration of other methods of rapid vitamin E supplementation.

Cost of neonatal care in the Trent region. S Hodges, R Fordham, DJ Field, C Normand, E Mason, and P Burton (Leicester and York).

There have been three previous studies in the UK assessing the economics of neonatal intensive care, all relating to regional units. In a one year prospective study the cost of neonatal care for the entire Trent region has been calculated. The number of days intensive care level I (ITU I), intensive care level II (ITU II) and special care (SC) (as defined by the British Association of Perinatal Paediatrics) were obtained for each unit in the region (13 SCBU, four subregional intensive care units). Unit accountants provided the cost of support services and hospital overheads and senior nursing and medical personnel provided details of the staffing establishment. A total cost per annum was then calculated for each unit. A previous study has suggested that ITU I is approximately twice as expensive as ITU II and six times more expensive than SC. Using this ratio the cost per day for each level of care in each unit was calculated.

The results, mean (and range) are summarised in the table.

Mean cost (£)	*ITU I*	*ITU II*	*SC*
All units (n=17)	554 (291–943)	277 (146–471)	92 (48–157)
Subregional ITU (n=4)	361 (291–415)	180 (146–208)	60 (48–69)
SC (n=13)	613 (395–942)	306 (196–471)	102 (64–153)

These results suggest that regional or subregional units are a more cost effective way of treating newborn infants requiring prolonged hospital care.

Anti-endotoxin therapy for fulminant meningococcal septicaemia: pilot study. A Thomson, J Sills, CA Hart, and F Harris (Liverpool).

Aims: to evaluate the possible benefits of anti-endotoxin therapy (AET) in fulminant meningococcal septicaemia (FMS).

Methods: during 1987 children with clinical evidence of FMS, as defined by a Glasgow meningococcal septicaemia prognostic score of >7, were identified prospectively, and later confirmed bacteriologically. In addition to conventional intensive therapy, patients received AET for two days, with intravenous polymyxin E (2 mg/kg daily) and immunoglobulin containing anti-endotoxin antibodies (Pentaglobin 5 ml/kg daily). Survival was compared with cases of FMS presenting between 1 January 1977 and 31 December 1986, ascertained from hospital records and scored retrospectively.

Results: of 34 cases of meningococcal septicaemia admitted in 1987 and 134 in 1977–1986, 32 had FMS. In 1987, 11 patients were treated with AET; eight (72·7%) survived. Of 21 patients, (19 during 1977–1986, and two during 1987), not given AET, six (28·6%) survived. AET was well tolerated.

Conclusions: treatment with AET in addition to conventional intensive therapy improves survival in FMS (p=0·019 by Fisher's exact test). A prospective double-blind placebo-controlled study is indicated. This would require 22 patients in each limb to show a difference at the 0·05 level with 95% power.

Surveillance of Kawasaki disease (KD) in the British Isles. SM Hall (Colindale).

BPA–CDSC joint surveillance of KD began on 1 January 1983 with the aim of describing its epidemiological and clinical characteristics in these islands. Initially paediatricians reported new cases on a precirculated standard form. From July 1986 cases were actively ascertained through the British Paediatric Surveillance Unit.

A total of 183 'classical' cases and 52 'atypical' cases were reported 1983–7. The change to active ascertainment caused a trebling of average annual totals compared with the preceding period of passive surveillance. 83% of 'classical' cases were under 5 (median age 31 months); the 'atypical' cases were older. There were marked geographical but not seasonal variations in incidence, and a significant excess of Oriental and Caribbean subjects. Case fatality rates of 2% and 9% and cardiac complication rates of 34% and 28% occurred among the 'classical' and 'atypical' cases respectively. Other complications included arthropathy (19%), diarrhoea (13%), and aseptic meningitis (10%). Thrombocytosis was consistent in both 'classical' and 'atypical' cases.

The clinical and most epidemiological features of KD in the British Isles 1983–7 were similar to those reported elsewhere. The incidence in 1987, however, was 4–6 times lower than in Europe or Canada, although comparable with that in USA. There is a need for increased diagnostic vigilance and awareness of atypical cases as the standard case definition for KD may be too restrictive.

Liver disease in cystic fibrosis (CF). RH Scott-Jupp, M Lama, and MS Tanner (Leicester).

Previous postmortem data suggests a prevalence of liver abnormality in CF rising steadily with age, but clinical prevalence data are lacking. A total of 506 CF patients (1–30 years) in Leicester, Birmingham, Nottingham, and Peterborough were reviewed seeking evidence of 'overt' liver disease—that is, splenomegaly, hard or irregular hepatomegaly, or varices; or of abnormal liver function tests. 'Overt' liver disease (LD) prevalence peaked in the second decade:

Age (years)	*0–5*	*6–10*	*11–15*	*16–20*	*21–25*	*25–30*	*Total*
Total	145	127	84	101	41	8	506
'Overt'	2	2	7	11	1	1	24
'Biochemical'	11	10	9	17	4	1	52

This suggests that LD is associated with death in teenage years. Eleven of the 80 CF deaths 1978–88 were in patients with LD, and occurred at median age 15 (range 8–17) years. One 25 year old received a triple transplant. Eighteen of 24 cases of overt LD, and 8/11 liver deaths, occurred in males. Presentations of overt LD were splenomegaly (3), hepatomegaly (7), hepatosplenomegaly (12), gallstones (1), abnormal LFTs (1). Varices were present in seven and bled in five. 'Biochemical' liver disease showed no sex predilection, did not peak in prevalence, and was absent in 5 children with overt LD.

Conclusions: LD in CF is not a function of longevity. In our study males were preferentially affected. LD is associated with death in the second decade, presents as portal hypertension, and is not predicted by abnormal LFTs.

The role of magnetic resonance imaging in investigating neurological disorders. AC Elias-Jones, T Jaspan, DH Mellor, and BS Worthington (Nottingham).

Magnetic resonance imaging (MRI) provides an additional powerful tool for investigating neurological disorders, but limited resources demand prudent selection for its use. We have attempted to seek guidelines for such careful application in a neurosciences unit.

Eighty children (41 males:39 females) aged 2 days–17 years (mean 9·2 years) were investigated by paired CT and MRI brain scans (group A, 48 cases) or paired CT myelograms and MRI spinal scans (group B, 32 cases), to compare the scans' usefulness in assessing a variety of neurological disorders.

In group A, 21 children had tumours (11 scans equivalent, nine MRI scans superior, one CT brain scan superior), five had suspected hydrocephalus (four both scans equal and positive, one both negative); eight had focal fits (both scans negative in seven, both positive in the eighth); both scans were positive in two cases of cerebral atrophy, and in two children with corpus callosal anomalies the MRI scan delineated the lesion better. In eight other varied neurological disorders both scans were negative in five, and the MRI scan was superior in three.

In group B, 18 cases had cord tethering (eight scans equal, in nine the MRI was better, and in one the CT was superior), and the MRI tended to be better where tethering involved a lipoma/lipomyelomeningocoele or syrinx. In five cases of spinal tumours or syrinx the MRI was superior in four and equivalent in the fifth. In three cases with bladder problems both scans were negative. In six cases with cervical or thoracic problems the scans were equal in three, and the MRI better in the other three.

Thus if cord tethering or syrinx is suspected an MRI scan is likely to be more informative. Similarly, if cerebral or spinal tumours are predicted an MRI scan is preferable, if available. In investigating bladder symptoms or focal fits, if the CT scan is negative, the MRI scan is unlikely to provide additional positive information.

Neurological morbidity in survivors of cardiac surgery in childhood. AG Stuart, DW Heaviside, AS Hunter, HH Bain, and JA Eyre (Newcastle upon Tyne).

Advances in surgical and anaesthetic techniques have led to a decrease in mortality from cardiac surgery but there is increasing concern about the neurological morbidity. We have reviewed the notes of all children undergoing cardiac surgery in the Regional Cardiothoracic Centre during May 1985–April 1987. In 312 children aged 1 day–15 years (median 2·5 years) 325 operations were performed: 188 cardiopulmonary bypass (CPB), 137 closed heart (CH). Follow up was from one month to three years (mean 1·3 years).

Within two weeks of operation 39 (12·5%) died and in total 60 (19%) died within the follow up period, 37 (20%) CPB and 16 (18%) CH. A total of 273 survived the immediate postoperative period: 158 CPB and 115 CH. Forty (15%) had neurological sequelae diagnosed, 22 (14%) CBP, and 17 (15%) CH. Peripheral neuropathies occurred in 2 (1%) CPB and 11 (10%) CH. CNS lesions were noted in 26 (10%): 20 (13%) CPB and six (5%) CH. These resulted in moderate or severe handicap in 13.

High risk factors for death or neurological sequelae were (i) prolonged cardiopulmonary bypass and aortic clamp times; 84 and 47 mins respectively for normal survivors, 126 and 62 mins for abnormal survivors and 157 and 88 mins for those who died $p<0{\cdot}001$; (ii) circulatory arrest which occurred in 12, four (30%) died, four (30%) had neurological sequelae; (iii) age <3 years. Postoperative mortality for children <3 years was 22% CBP and 11% CH compared with 5% and 4% respectively for those >3 years ($p<0{\cdot}01$). In the survivors neurological sequelae occurred in 26% CPB and 12% CH (<3 years) and 5% and 11% respectively for >3 years ($p<0{\cdot}01$).

There remains a high incidence of neurological morbidity in survivors of cardiac surgery despite intensive postoperative care. More research is needed into the pathophysiology of the brain damage so that appropriate measures can be taken to minimise the cerebral consequences of cardiac surgery.

The prevalence of Campylobacter pylori in Gambian children and its relationship to malnutrition. JE Thomas, PB Sullivan, EJ Eastham, G Neale, P Mackie (Newcastle upon Tyne and Cambridge).

Malnutrition in children in the developing world is often associated with achlorhydria. *C pylori* is known to cause gastritis, with transient achlorhydria following acute infection. *C pylori* is rare (1%) in children <10 years of age in this country, but may be common in children in the tropics. We therefore investigated the prevalence of *C pylori* in Gambian children, and its relationship to malnutrition.

The study was divided into two phases: *Phase 1*: 20 consecutive children undergoing upper GI endoscopy aged 5 months–9 years. Sixteen had active gastritis, and *C pylori* was seen in 11 cases. Fourteen of the patients with gastritis had high circulating specific antibodies against *C pylori* as measured by ELISA. A high specific IgG titre of >1:10,000 was found in active infection with gastritis. *Phase 2*: A cohort of 361 children, aged <5 years, from one village had serum anti *C pylori* IgG assayed, and height, weight, and age recorded. The prevalence of specific IgG titres of >1:10,000 increased from 14% in the 0–20 month age group to 46% in the 40–60 month group.

In children aged <30 months, specific IgG titres >1:10,000 were found in 11/39 (28%) whose height/weight ratio was <75% mean for age, and in only 14/116 (12%) children whose height/weight ratio was >75% for age ($p<0{\cdot}025$). No such difference was found in older children. These data show that *C pylori* is common in young Gambian children, and that it is associated with malnutrition.

Evaluation of the usefulness of neonatal screening in cystic fibrosis. G Owen, S Chatfield, HC Ryley, MC Goodchild, and P Weller (Cardiff and Birmingham).

A study was set up in January 1985 to evaluate the effect of neonatal screening for cystic fibrosis (CF) by immunoreactive trypsin (IRT). The tests have taken place on alternate weeks only, in Wales and the West Midlands, so that two groups, screened and unscreened, have been generated in each region. In addition, we have compared the effects of continuous flucloxacillin and intermittent antibiotics. Detailed clinical and biochemical tests are carried out annually on each child.

By the end of October 1988, 173 931 infants have been screened, of whom 50 were found to have CF. During the same period, a further 44 CF infants and young children were detected on clinical criteria. Clinical comparison reported here is between screened and unscreened patients and excludes those who have presented with meconium ileus or who had a family history of CF.

Analysis of age at diagnosis showed a significant difference: 67±29 days for screened, 213±229 days for the unscreened, $p<0{\cdot}001$. Clinical values and scores, at one and two years, tended to be better for the screened than the unscreened, but differences were not significant. Neither regime of antibiotic treatment showed an advantage at the age of 2 years.

A gene for atopy and atopic asthma located on chromosome 11q13. WOCM Cookson, PA Sharp, and JM Hopkin (Oxford).

Atopy, the state of allergic responsiveness to inhaled proteins, underlies the common disorders of asthma and allergic rhinitis. Although recognised as familial, the genetic basis for atopy has not previously been elucidated. We first studied the parents of 20 randomly selected atopic asthmatics aged 12–15 years. Eighteen children (90%) had at least one atopic parent, so that 63% of the parents were atopic, in contrast with the 25% of parents of controls (who were admitted to hospital with non-atopic illnesses) ($\chi^2=11{\cdot}2$, $p<0{\cdot}005$). In five extended families, 57 of 92 children resulting from atopic/non-atopic matings and 16 of 25 children from atopic/atopic matings were themselves atopic, consistent with the segregation of an autosomal dominant trait.

Linkage analysis with DNA restriction fragment length polymorphisms located the atopy gene to chromosome11q13 (probe p λ MS.51: a maximum lod score of 4·13 at a recombination fraction of 0·13).

Atopy is a genetic illness: characterisation of the atopy gene and its product may permit more successful pharmaceutical control of the common and disabling diseases of asthma and rhinitis.

High frequency oscillation: an investigation into its use in the surfactant deficient lung. E O'Callaghan and A Padkin (Bristol and Toronto).

High frequency oscillation (HFO) is a new ventilation technique which, in the treatment of respiratory distress syndrome (RDS), has been shown to reduce hyaline membrane formation and increase O_2 delivery and CO_2 removal when compared with conventional mechanical ventilation (CMV).

The pressure/volume relationship in the surfactant deficient lung exhibits hysteresis. To use HFO, expansion of the lungs must first take place using a brief sustained inflation (SI) to a mean airway pressure (MAP) which exceeds the opening pressure. The MAP can then be reduced to a maintenance pressure slightly greater than the critical closing pressure. The aim of our project was to determine the opening and critical closing pressure using an animal model.

Five adult rabbits were studied. Following anaesthesia and tracheostomy saline lung lavage was performed and ventilation maintained on CMV for 90 minutes. HFO was then initiated with a SI for 15 seconds at a MAP of 30 cm H_2O. The MAP was then decrementally reduced to the point of lung collapse, as indicated by a PaO_2 measurements. Subsequently, to determine opening pressure, MAP was increased in steps until lung re-expansion occurred.

HFO was seen to confer a substantial benefit in oxygenation compared with CMV. On HFO critical closing pressure lay between 14 cm H_2O and 10 cm H_2O. The opening pressure was approximately 24 cm H_2O.

This experiment defined the opening and critical closing pressures of the surfactant deficient lung in an animal model. A more informed choice of ventilator pressures for both SI and maintenance on HFO is now possible.

Screening for short stature—The Wessex Growth Study. L Voss, J Walker, H Lunt, T Wilkin, and P Betts (Southampton).

The Wessex Growth Study is a longitudinal community survey of all 5 year olds <3rd centile for height, entering school from 1985–6 and 1986–7. The aim is to monitor the growth, psychological development, and school progress of very small children and to compare those on GH therapy with an untreated group and with matched 'normal' controls. Results of screening the 1985–6 entrants for short stature, and growth patterns over the first 12 months are described.

Only 1·3% of entrants fell <3rd centile, as defined by Tanner and Whitehouse, suggesting a strong secular trend and the urgent need to revise UK growth charts. A few children had underlying pathology (8%) but many more had small parents (34%), delayed bone age (42%), or were small for dates (44%). As many as one in four may be suffering from psychosocial deprivation. Preliminary data shows that the small children are behind their controls at age 5 in language and number skills.

Thirty eight percent had poor 12 month velocities (<25th centile), including many whose cause of short stature appeared evident (for example, familial). Twenty percent had two successive six month velocities <25th centile.

Although as a group the short children grew more slowly than their controls, the velocity in 88% of cases however lay within the control range. Furthermore, the lack of correlation between two successive six and even 12 month velocities suggests the need for great caution in both diagnosing growth failure and interpreting response to treatment in any individual.

Trends in the birth prevalence of cerebral palsy (CP). T Cooke, POD Pharoah, L Rosenbloom, and RWI Cooke (Liverpool).

A register of children with cerebral palsy born in 1966–1984 to mothers resident in the Mersey region has been compiled from several different data source to ensure completeness of ascertainment. The birth prevalence trend covering the first part of this period—that is, 1966–1977—has already been reported.[1] The present report extends the trend to cover the period 1978–1984. The prevalence of CP among normal birthweight infants (>2500 g) has remained constant throughout the period of study. Among low birthweight (1501–2500 g) and very low birthweight infants (<1500 g) the prevalence of CP has shown a 2–3 fold rise. It has occurred among all types of CP but has been most striking among the diplegias.

In contrast to the earlier report when 8% of infants weighing 2500 g or less with CP received artificial ventilation, in the new cohort 56% were ventilated. This may be a consequence of increased use of neonatal intensive care.

Reference

[1] Pharoah POD, Cooke T, Rosenbloom L, Cooke RWI. Trends in birth prevalence of cerebral palsy. *Arch Dis Child* 1987;**62:** 379–84.

Randomised trial of treatment for posthaemorrhagic ventricular dilatation. A Whitelaw (Oxford).

Very low birthweight infants who develop progressive ventricular dilatation following intraventricular haemorrhage (IVH) are at high risk of disabling neuromotor impairments. As raised CSF pressure may impair cerebral perfusion, we hypothesised that early drainage of CSF might improve the prognosis.

A collaborative study in 15 neonatal units in England, Eire, and Switzerland enrolled 157 infants whose ventricular width had enlarged to 4 mm over the 97th centile after IVH. One group was randomised to immediate intervention with serial lumbar punctures or ventricular taps. Treatment was delayed in the other group until two weeks excessive head growth had occurred or symptomatic raised intracranial pressure developed. Thirty infants died and six could not be followed. A total of 121 infants have had full assessment by the same developmental paediatrician. There was no difference in the Griffiths Developmental Subscales or numbers of infants with severe disabilities when the two treatment groups were compared. Seven out of 77 infants treated with early taps developed ventriculitis (without surgery) and three of these died with ventriculitis. Only three out of 80 conservatively managed infants developed ventriculitis (without surgery) and none died with ventriculitis. Early taps did not significantly reduce the need for later shunting. Thus early tapping conferred no advantage in neurodevelopmental outcome and may carry an increased risk of CSF infection.

National survey of childhood onset diabetes, 1988. JD Baum, MA Metcalfe, EAM Gale, and RJ Jarrett (Bristol and London).

There is no accurate national epidemiological data on childhood onset diabetes in the British Isles. Through the facilities of the British Paediatric Surveillance Unit (BPSU) new cases have been notified for the calendar year 1988. A total of 1007 cases have been reported to the BPSU so far (mid-November 1988) by 312 paediatricians, seven physicians, and seven parents. There are considerable regional differences in the incidence of reported cases: for example, the incidence in East Anglia is more than double that of the adjacent North West Thames (11·6 cf 4·4 per 100 000 aged <16 years respectively). There have been noteworthy monthly variations in incidence with most diagnosed in February (109), and falling sharply from April to May (97 to 70). Sixty one cases (so far) were diagnosed in June; data for more recent months is being collected. Some detailed information is currently available on 615 of the 1007 children. There is no sex difference in incidence (males 316, females 299). The mean age at diagnosis is 8·7 years (range 0·1–15·9). 24% of cases are under five years. To date 281 parental questionnaires have been returned. This small number reflects the natural time sequence of the study: there is no indication of parental unwillingness to reply. The questionnaires will provide information on family history, social and educational background, and details such as infant feeding. It is anticipated that by April 1989 the great majority of cases will have been identified, and substantial information available for analysis.

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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

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Archives of Disease in Childhood, 1989, **64,** 1223–1224

Annotation

Fragile X mental retardation

It used to be said that diabetes was a geneticist's nightmare. The number one nightmare position may well have been taken over by fragile X mental retardation, which behaves deceptively as if it is caused by a standard X linked gene, but can be passed through completely normal males, and although it can be diagnosed by cytogenetic techniques, it has to be on a good day when all the laboratory conditions are optimal! It has also been mapped on the X chromosome by extensive efforts using the new molecular genetic techniques—although the map is only about as good as saying that Birmingham is somewhere between London and Manchester.

This is not to say that progress has been lacking in the understanding of this elusive condition or that the level of research activity is not intense. The incidence of the condition is so high that it is thought to be the second most common genetic cause of mental retardation after Down's syndrome. Reliable estimates of prevalence read like the sort of over-exaggeration seen in grant applications: 0·3–1/1000 in males and 0·2–0·6/1000 in females, but these numbers have been verified by several studies.[1–3]

The term fragile X retardation derives from the unusual appearance of the distal portion of the long arm of the X chromosome in a proportion of cells of affected individuals. At metaphase the two chromatids appear to be thinned to a thread with the terminal tips hanging on like a pair of inverted commas (figure). Such thinning of the chromatin is termed a fragile site. Special culture conditions are needed for the cells to express the fragile site—low folate and thymidine or treatment with fluorodeoxyuridine or methotrexate. Even then the fragile X chromosome is not seen in every cell. In affected males 4–50% of cells may show the fragile site, in female gene carriers of the condition the proportion is less, and in about 50% of these females the fragile X chromosome cannot be detected at all.[4]

The condition causes a non-specific form of mental retardation—that is, without major dysmorphic features or severe neurological abnormalities. Before puberty it is probably impossible to make a confident diagnosis clinically, although affected children may be slightly taller than average, with a larger than average head circumference, and perhaps loose joints. Developmental assessment in boys ranges from 20–70 and speech may be particularly affected. A characteristic speech pattern has been noted—so called 'cluttering' or hurried, repetitive sentences that come out in a rush. The incidence of the condition has been found to be increased in children with autistic features and ranges from 0–15% of males in different studies.[5] The incidence in autistic females may be lower.[6] After puberty the testes are usually significantly enlarged and the face is long with a large, squared off mandible and large ears.

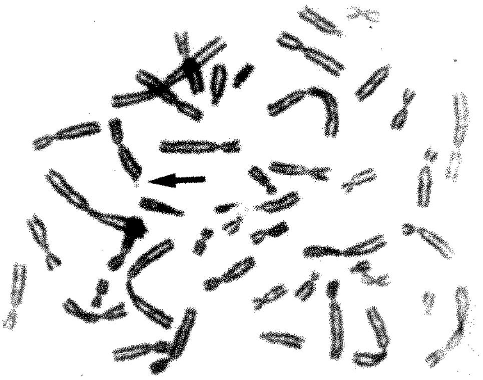

Figure *Fragile X syndrome—what the cytogeneticist sees. In this unbanded chromosome preparation from one cell of an affected male the arrow points to the fragile site on the X chromosome. The end of the chromosome is separated from the proximal part by a thinned segment of chromatin—the fragile site itself.*

Approximately 30% of female gene carriers have mild to moderate developmental delay, with occasional severely affected individuals. There is some correlation between the percentage of cells expressing the fragile X chromosome and the degree of retardation in females.

Treatment with high doses of folic acid has been tried, but no significant improvement of behaviour or performance has been recorded in blind trials.[7]

Prenatal diagnosis can be carried out by cytogenetic techniques. The most reliable method is to look at the chromosomes of fetal lymphocytes obtained by fetal blood sampling. Cells from amniotic fluids or a chorionic villus sample can also be studied; however, techniques for encouraging the expression of the fragile site are at present less reliable in these tissues.[7] A further complication arises if a female fetus is detected that shows a significant proportion of cells with a fragile X chromosome. In this case there may be a 30% chance of mild to moderate developmental delay—a situation that makes decision about termination difficult for the parents and clinicians.

One of the alternative names for the condition, Martin-Bell syndrome, comes from a report of a very large pedigree studied before the fragile X chromosome was discovered.[8] Subsequent cytogenetic analysis has shown the fragile X chromosome in affected members. The family reported illustrates some of the unusual genetic features of the condition. A cursory look at the pedigree reveals affected males linked by normal or mildly retarded females—standard 'semi-dominant' X linked inheritance. However, closer inspection shows that there are also completely normal males in the family who appear to have passed on the gene to their normal daughters, who then go on to have affected sons. These 'normal transmitting males' must carry an abnormality at the fragile X locus but it is not certain whether this is the full mutation, which is masked by genes at separate loci or by other genetic interactions, or whether they carry a premutation that predisposes to the generation of the full mutation when it is passed through their normal daughters to their grandsons. In any event, it seems as though there must be novel genetic mechanisms operating at the fragile X locus to explain the unusual inheritance pattern.

Molecular genetic studies have shown polymorphic DNA markers close to the fragile X locus that might potentially be used for prenatal diagnosis or for carrier detection, however, even here there are difficulties. There is evidence that some DNA markers are closely linked in some families (or parts of families) but not in others, making them unreliable for clinical use. When new, closer markers are discovered, many families will have to be studied before the risk of similar 'linkage heterogeneity' can be ruled out and the probes can be used clinically.[4] Meanwhile, the only reliable means of prenatal diagnosis is by additional examination of fetal chromosomes and there is no completely reliable method of excluding carrier status in females who don't express the fragile X chromosome.

The general paediatrician must suspect the condition in a child of either sex with non-specific mental retardation, even in the absence of a family history. Requests for cytogenetic analysis must mention the possibility of fragile X syndrome and cases must be selected carefully. Appreciable microcephaly, dysmorphic features, or abnormal neurological features make the diagnosis very unlikely and the cytogenetic laboratory should not normally be asked to carry out fragile X analysis on these cases. Even with careful selection, complete ascertainment of all cases eligible for fragile X analysis in a region would overwhelm most cytogenetic laboratories without special resources. A planned programme, giving initial priority to cases where family members are envisaging further children, may be necessary.

Families of affected children should be referred to genetic centres as the complex inheritance pattern and problems with carrier detection and prenatal diagnosis make genetic follow up far from straightforward.

References

[1] Webb TP, Bundey SE, Thake AI, Todd J. Population incidence and segregation ratios in the Martin-Bell syndrome. *Am J Med Genet* 1986;**23**:573–80.

[2] Turner GH, Robinson H, Laing S, Purvis-Smith S. Preventive screening for the fragile X syndrome. *N Engl J Med* 1986;**315**: 607–9.

[3] Kahkonen M, Alitalo T, Airaksinen E, *et al.* Prevalence of the fragile X syndrome in four birth cohorts of children of school age. *Hum Genet* 1987;**77**:85–7.

[4] Froster-Iskenius U, Patterson MW, Bell MV, Bloomfield J, Davies KE. Molecular analysis of the fragile X chromosome. *Q J Med* 1988;**69**:755–63.

[5] Brown WT, Jenkins EC, Cohen IL, *et al.* Fragile X and autism: a multicenter survey. *Am J Med Genet* 1986;**23**:341–52.

[6] Blomquist HK, Bohman M, Edvinsson SO, *et al.* Frequency of the fragile X syndrome in infantile autism. *Clin Genet* 1985;**27**:113–7.

[7] Neri G, Opitz JM, Mikkelsen M, Jacobs PA, Davies KE, Turner GH. Conference report: third international workshop on the fragile X and X-linked mental retardation. *Am J Med Genet* 1988;**30**:1–29.

[8] Martin JP, Bell J. A pedigree of mental defect showing sex-linkage. *J Neurol Neurosurg Psychiatry* 1943;**6**:154–7.

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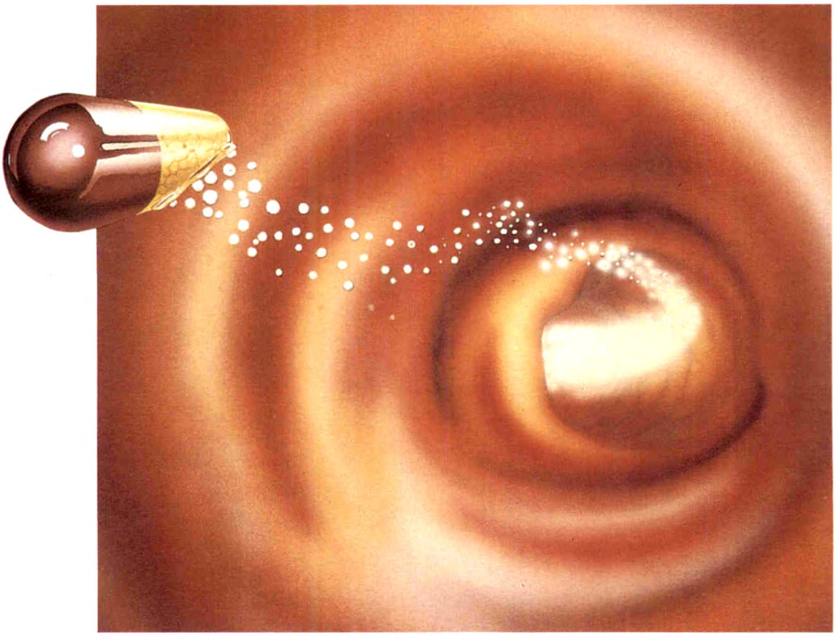

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Archives of Disease in Childhood, 1989, **64**, 1225–1230

Original articles

Early experience of heart-lung transplantation

R L SMYTH, T W HIGENBOTTAM, J P SCOTT, J P McGOLDRICK, B WHITEHEAD,* P HELMS,*
M DE LEVAL,* AND J WALLWORK

*Heart-Lung Transplant Research Unit, Papworth Hospital and *The Hospital for Sick Children, Great Ormond Street, London*

SUMMARY We report our experience of heart-lung transplantation for the treatment of children with terminal respiratory disease. Between May 1987 and October 1988 we performed heart-lung transplantation in five children under the age of 16 (age range 11–15). All the patients were severely disabled by dyspnoea and hypoxia. Two had primary pulmonary hypertension, two cystic fibrosis, and one had Eisenmenger's syndrome.

All five children are alive and well five to 17 months after operation and have returned to activities normal for their age. Three of the five patients had episodes of infection after operation. These were staphylococcal pneumonia, herpes simplex pneumonitis and, in one of the patients with cystic fibrosis, persistent purulent sputum. The mean number of episodes of rejection per child was 2·7 per half year. Heart-lung transplantation is a practical treatment for children in these disease groups with terminal respiratory failure.

In 1981 after the introduction of cyclosporin and the development of a new surgical technique, heart-lung transplantation began to yield satisfactory results.[1] First introduced as a treatment for pulmonary vascular disease, heart-lung transplantation was extended to treat end stage lung disease[2] and then cystic fibrosis.[3] Since 1984 we have performed 51 heart-lung transplantations. As experience increased and survival improved[4] recipient selection was expanded to include older and younger patients. We report here our experience in five children under the age of 16 years (range 11–15 years) who had a heart-lung transplantation between May 1987 and October 1988.

Patients and methods

Between March 1985 and October 1988, 33 children below the age of 16 were referred for assessment of their suitability for heart-lung transplantation. Thirty of these have been assessed and 15 were placed on the active waiting list for transplantation. Ten were considered to be suitable but not sufficiently disabled to require transplantation and were placed on a 'provisional' waiting list. Five patients were felt to be unsuitable, four because they were too well and the other because of profound intellectual difficulties. Two of the 10 patients for whom donor organs did not become available died, both within two months of assessment, and four patients died waiting to be assessed. Suitable donor organs became available for five of the 15 patients accepted.

Preoperative assessment included determination of the degree of disability, including requirement for home oxygen, evidence of other organ malfunction, and the presence of right ventricular failure. Respiratory function testing included spirometry (Vitalograph Ltd), single breath transfer for carbon monoxide (P K Morgan), measurement of lung volumes by whole body plethysmography (Jaeger Bodyscreen II Body Box, Eric Jaeger GmbH and CoKG), and helium dilution (Spectromed Ltd). All patients underwent a 12 minute walk with continuous arterial oxygen saturation measurement using pulse oximetry (Datascope Accusat Pulse Oximeter, Datascope). The 12 minute walking distance was measured together with the minimum arterial oxygen saturation achieved during this exercise.[5]

Donor and recipient matching was, in the first instance, by ABO blood group compatibility and cytomegalovirus antibody status. The donor and recipient were matched for size by taking measurements of the height of the thoracic vertebral column and width of the rib cage on the chest radiograph.[6]

Donor lungs were considered suitable if they had normal compliance (peak inspiratory pressure below

2·67 kPa, tidal volume of less than 15 ml/kg, respiratory rate of between 10 and 14 breaths/minute), normal gas exchange (arterial partial pressure of oxygen greater than 15 kPa with fractional inspired oxygen of 30%), and no evidence of pulmonary infection.[4] As these criteria are so precise less than 20% of heart donors are acceptable as lung donors.[7]

The technique for heart-lung transplantation has been previously described.[8 9] All grafts were distantly procured at the donor hospital. The ischaemic times were 150–188 minutes. Immunosuppression was maintained with oral cyclosporin and azathioprine. The dose of cyclosporin was adjusted to give a whole blood concentration of less than 1000 μg/ml, a plasma concentration less than 300 μg/ml, and a concentration of azathioprine to keep the total white cell count above $5\cdot0\times10^9$/l. Rejection episodes were treated with intravenous methylprednisolone 500 mg, daily for three days followed by oral prednisolone 1 mg/kg/day reducing to 5–10 mg/day over a period of 10 days. Patients remained on this dose until the episode of rejection was deemed on clinical or histological grounds, or both, to have resolved.

Postoperatively patients were monitored clinically, radiologically, and by pulmonary function. A microspirometer (Micromedical Ltd) was used to record forced expiratory volume in one second (FEV$_1$) (figure). Fever, dyspnoea, crackles on auscultation, radiologic shadows, and a fall in FEV$_1$, suggesting lung rejection or infection, were an indication to perform fibreoptic bronchoscopy and transbronchial biopsy.[10–12] Routine transbronchial biopsy was performed at three months and then yearly after operation. Routine endomyocardial biopsies do not contribute to patient management and were not performed.[13] Rejection was distinguished from infection by the presence of perivascular lymphocytic infiltrates.[11] Viral pneumonitis was confirmed histologically by the presence of diffuse alveolar damage in association with viral inclusion bodies.[10]

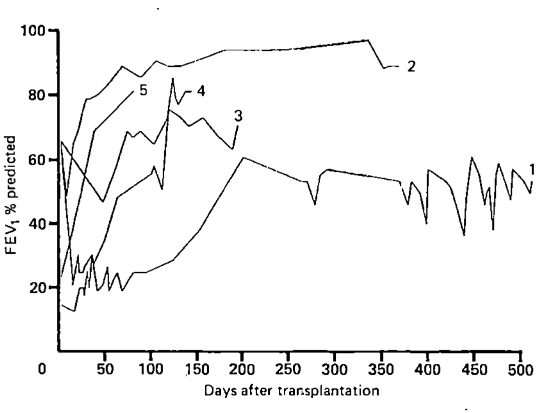

Figure *Forced expiratory volume in one second (FEV$_1$) expressed as a percentage of the predicted[14] plotted against time since transplantation for each patient.*

Results

Preoperative details of the five patients who received heart-lung transplants are shown in table 1. The FEV$_1$ measured was compared with values predicted for sex and height in children.[14] All patients were severely disabled with a 12 minute walking distance of less than 350 metres. Both patients with cystic fibrosis required continuous oxygen treatment and had evidence of right ventricular failure requiring diuretic treatment. There was no evidence of renal or hepatic dysfunction and fasting blood glucose concentrations were normal in all cases. The three patients with pulmonary vascular disease had cardiac catheterisation performed as part of their assessment. All had raised pulmonary artery pressure and reduced cardiac output (table 2).

The preoperative diagnosis in patient 2 was thought to be Eisenmenger's syndrome secondary to an ostium primum atrial septal defect. On examination of the explanted organs no intracardiac shunt was shown and a diagnosis of primary pulmonary hypertension was made.

Mean time from acceptance onto the waiting list and transplantation was 2·4 months. The predicted total lung capacity for the donor[14] and the measured total lung capacity for the recipient showed that satisfactory size matching was achieved (table 3). Postoperative complications are shown in table 4. Patient 1 was weaned off cardiopulmonary bypass with difficulty because of left ventricular dysfunction possibly associated with a subendocardial infarction in the donor heart. The heart failure was refractory to β agonists, but enoximone (Merrell Dow Pharmaceuticals Ltd), a phosphodiesterase inhibitor, restored haemodynamic stability and there were no long term cardiovascular sequelae. The early postoperative course in patient 4, who had had two previous thoracotomies, was complicated by recurrent bleeding necessitating surgical intervention on three occasions. Serial spirometric studies showed an early postoperative fall in FEV$_1$ (figure), which subsequently rose, as in patient 2, to around 100% predicted value. In patients 1 and 3 this increase in FEV$_1$ was delayed by episodes of rejection. There was a mean of 2·7 episodes of rejection per child per six months.

Table 1 *Details of sex, diagnosis, and age at time of transplant, and assessment details for each patient treated with heart-lung transplantation*

Patient No (sex)	*Diagnosis*	*Age at transplant*	*FEV$_1$ (% predicted)*	*Blood gases in air (kPa)*		*12 minute walk*	
				pCO$_2$	*pO$_2$*	*Distance walked (metres)*	*Lowest arterial oxygen saturation (%)*
1 (M)	Primary pulmonary hypertension	12	64	*	*	310	*
2 (F)	Primary pulmonary hypertension	15	53	*	*	Unable to perform walk	
3 (F)	Cystic fibrosis	11	16	7·2	7·2	240	79
4 (F)	Eisenmenger's syndrome	15	66	5·4	3·8	300	68
5 (F)	Cystic fibrosis	14	19	7·4	5·9	260	74

*Data not available.

Table 2 *Data from cardiac catheterisation on three patients with pulmonary vascular disease*

	Patient No		
	1	*2*	*4*
Time before transplantation (months)	3	18	1
Mixed venous oxygen saturation (%)	57	59	55
Mean pulmonary artery pressure (kPa)	13·50	9·33	6·7
Cardiac index (l/min/m^2)	1·9	1·1	1·9*

*Pulmonary flow index.

Table 3 *Total lung capacity (in litres), measured by whole body plethysmography (patients 1–4) and by helium dilution (patient 5), predicted and measured for each recipient compared with the predicted total lung capacity[14] for each donor*

Patient No	*Recipient*		*Donor-predicted*
	Predicted	*Measurement*	
1	3·68	3·8	3·75
2	4·46	4·0	4·53
3	2·78	3·41	2·4
4	3·59	2·97	3·47
5	2·73	1·93	2·23

The first patient was cytomegalovirus antibody negative, but received organs from a donor who was positive as the result of a false negative latex agglutination test performed at the donor hospital. He was given prophylactic hyperimmune globulin when the mismatch was identified. On day 32 he developed increasing shortness of breath and a decline in respiratory function tests (figure). Cytomegalovirus pneumonitis was suspected, a transbronchial biopsy was performed and he was treated with the antiviral agent ganciclovir (Cymevene, Syntex). Histological examination showed evidence of acute rejection without any of the typical changes of cytomegalovirus pneumonitis. He was then treated for rejection, which resulted in symptomatic improvement and a rise in FEV$_1$. There was no rise in antibody to cytomegalovirus, and viral cultures were negative.

Patient 4 presented on day 50 with florid herpes simplex lesions in the mouth, a spiking temperature, and radiographic features of pneumonitis. The specimen obtained at transbronchial biopsy, although not specific for herpes simplex pneumonitis, showed viral pneumonitis and the patient responded promptly to treatment with intravenous acyclovir.

Patients 4 and 5 had evidence of growth delay preoperatively; heights were below the 10th centile

Table 4 *Postoperative complications*

Patient No	*Early postoperative complications*	*Episodes of infection*	*No of episodes of rejection**	*Time since heart-lung transplantation (months)*
1	Left ventricular dysfunction	Staphylococcal pneumonia	5	17
2			3	13
3		Persistent sputum infection	5	7
4	Bleeding from the chest wall	Herpes simplex pneumonitis	4	5
5			4	4

*Diagnosed by histological examination.

for age and carpal bone ages were three and four years, respectively, behind their chronological ages. Patient 1, whose height at the time of heart-lung transplantation was above the 50th centile, 15 months later has a height just above the 25th centile, probably the effect of repeated courses of prednisolone required to treat rejection episodes.

Discussion

After success in adults, cardiac transplantation is now an accepted treatment for children with end stage cardiac disease.[15–17] Our early experience suggests that heart-lung transplantation is an acceptable procedure in children.

The number of children who may benefit from heart-lung transplantation may be assessed by examining the mortality statistics for the age group 5–15 in England and Wales. In 1986 the number of deaths for cystic fibrosis, Eisenmenger's syndrome, and primary pulmonary hypertension, were 40, 17, and three respectively. The number of patients represented with primary pulmonary hypertension may be an underestimate because, as our second case clearly illustrates, it may not be possible to diagnose it in life. This may also be true for Eisenmenger's syndrome where the diagnosis is frequently omitted from death certificates.

Patients are selected if they are considered to have a poor prognosis. In primary pulmonary hypertension, prognosis appears to be associated with low mixed venous oxygen saturation ($S\bar{v}O_2\%$). Fuster *et al* have shown that patients with an $S\bar{v}O_2\%$ below 63% have only a 17% chance of surviving untreated for three years, and those with an $S\bar{v}O_2\%$ of 63% or above have a 55% chance of surviving this period.[18] Survival in untreated Eisenmenger's syndrome is more difficult to predict and we have been guided largely by the patient's symptoms. We are currently evaluating the minimum arterial oxygen saturation and distance walked in the 12 minutes as an indication of cardiorespiratory disability.[5] In heart disease a raised pulmonary vascular resistance precludes heart transplantation,[15] and for these patients heart-lung transplantation is a therapeutic option.

Hypoxic hypercapnic respiratory failure associated with right axis deviation on the electrocardiogram is an ominous sign in cystic fibrosis.[19] The FEV_1, a further prognostic indicator,[20] was below 30% of the predicted value in all of the patients with cystic fibrosis accepted onto our waiting list.[3]

Contraindications to heart-lung transplantation include other organ dysfunction. This is particularly relevant in patients with cystic fibrosis. Evidence of liver disease makes surgery hazardous because of clotting abnormalities and has implications for long term survival. Such patients may be considered for combined heart, lung, and liver transplantation.[21] Previous cardiothoracic surgery heightens the risk of bleeding postoperatively. Previous pleurectomy or pleurodesis are currently contraindications to surgery, but a previous thoracotomy for the correction of cardiac anomalies as in patient 4, or lobectomy, are not contraindications. High dose steroid treatment delays wound healing and we reduce treatment to the minimum dose possible while the patient is awaiting the transplant.

Infection and rejection are the major problems encountered in long term patient management. Monitoring of lung function allows early detection of infection and rejection,[22] and the diagnosis is confirmed by transbronchial biopsy.[12] Primary cytomegalovirus pneumonitis, which is a common cause of death in heart-lung transplantation, occurs when cytomegalovirus antibody negative recipients receive organs from donors who are antibody positive. A rapid test of cytomegalovirus antibody status became available in 1985 and has enabled us to ensure that cytomegalovirus negative recipients receive organs only from negative donors.[23] Since this policy was adopted there have been no further deaths from organ transmitted cytomegalovirus disease.[24]

In our series of 51 recipients of heart-lung transplants we have had five cases of herpes simplex pneumonitis. Herpes simplex pneumonitis has been previously reported in recipients of heart-lung transplants, but proved fatal.[25] The prompt diagnosis by transbronchial biopsy and early treatment with acyclovir contributed to a successful outcome in patient 4.

The actuarial survival of 78% and 68% at one and two years respectively that we have reported for all heart-lung transplant recipients supports an optimistic outlook for transplantation in children.[4] Major concerns in the paediatric age group relate to chronic rejection and the long term side effects of immunosuppression. We have shown that the development of obliterative bronchiolitis is related to previous inadequately treated episodes of rejection.[26] Therefore adequate immunosuppression and early detection and treatment of rejection episodes should improve survival. There is a significant long term morbidity related to the use of both cyclosporin and corticosteroids. Morphological changes in the kidney after treatment with cyclosporin include interstitial fibrosis and glomerular sclerosis, which may be related to a cyclosporin induced reduction in renal blood flow and glomerular filtration rate.[27] We use steroids routinely only for the treatment of rejection episodes and so would anticipate that steroid induced growth suppression will be a problem only in that group of patients, of whom patient 1 is a typical example, who experience recurrent episodes of rejection.

Heart-lung transplantation is acceptable treatment for children with terminal respiratory disease. Although information on long term survival is not yet available, the improved quality of life in the short term in the children we have treated is encouraging.

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References

[1] Reitz B A, Wallwork J, Hunt S A, *et al.* Heart-lung transplantation. Successful therapy for patients with pulmonary vascular disease. *N Engl J Med* 1982;**306**:557–64.

[2] Penketh A, Higenbottam T, Hakim M, Wallwork J. Heart and lung transplantation in patients with end-stage lung disease. *Br Med J* 1987;**295**:311–4.

[3] Scott J P, Higenbottam T W, Penketh A R L, Hodson M, Stewart S, Wallwork J. Heart-lung transplantation for cystic fibrosis. *Lancet* 1988;**ii**:192–4.

[4] Hutter J A, Despins P, Higenbottam T W, Stewart S, Wallwork J. Heart-lung transplantation: better use of resources. *Am J Med* 1988;**85**:4–11.

[5] McGavin C R, Artininti M, Nave H, McHardy G J R. Dyspnoea disability and distance walked: comparison of estimates of exercise performance in respiratory disease. *Br Med J* 1978;**ii**:241–4.

[6] Hakim M, Higenbottam T W, Bethune D, *et al.* Selection and procurement of combined heart and lung grafts for transplantation. *J Thorac Cardiovasc Surg* 1988;**95**:474–9.

[7] Jamieson S W, Baldwin J, Stinson E B, *et al.* Clinical heart-lung transplantation. *Transplantation* 1984;**37**:81–4.

[8] Jamieson S W, Stinson E B, Oyer P E, Baldwin J C, Shumway N C. Operative technique for heart-lung transplantation. *J Thorac Cardiovasc Surg* 1984;**87**:930–5.

[9] Wallwork J, Jones K, Cavarocchi N, Hakim M, Higenbottam T W. Distant procurement of organs for clinical heart-lung transplantation using a single flush technique. *Transplantation* 1987; **44**:654–8.

[10] Higenbottam T W, Stewart S, Penketh A, Wallwork J. The diagnosis of lung rejection and opportunistic infection by transbronchial lung biopsy. *Transplant Proc* 1987;**19**:3777–8.

[11] Stewart S, Higenbottam T W, Hutter J A, Penketh A R L, Zebro T J, Wallwork J. Histopathology of transbronchial biopsies in heart-lung transplantation. *Transplant Proc* 1988;**20**: 764–6.

[12] Higenbottam T W, Stewart S, Penketh A R L, Wallwork J. Transbronchial lung biopsy for the diagnosis of rejection in heart-lung transplant patients. *Transplantation* 1988;**46**:532–40.

[13] Higenbottam T W, Hutter J A, Stewart S, Wallwork J. Transbronchial biopsy has eliminated the need for endomyocardial biopsy in heart-lung recipients. *Journal of Heart Transplantation* 1988;**7**:435–9.

[14] Cotes J E. Lung function throughout life; determinants and reference values. *Lung function.* 4th ed. London: Blackwell, 1979:340.

[15] Fricker F J, Griffith B P, Hardesty R L, *et al.* Experience with heart transplantation in children. *Pediatrics* 1987;**79**:138–46.

[16] Addonizio L J, Rose E A. Cardiac transplantation in children and adolescents. *J Pediatr* 1987;**111**:1034–8.

[17] Starnes V A, Stinson E B, Oyer P E, *et al.* Cardiac transplantation in children and adolescents. *Circulation* 1987;**76**:(suppl V) V.43–7.

[18] Fuster V, Steele P M, Edwards W D, Gersh B J, McGoon M D, Frye R L. Primary pulmonary hypertension: a natural history and the importance of thrombosis. *Circulation* 1984;**70**:580–7.

[19] Siassi B, Moss A J, Dooley R R. Clinical recognition of cor pulmonale in cystic fibrosis. *J Pediatr* 1971;**78**:794–805.

[20] Bishop J M, Cross K W. Physiological variables and mortality in patients with various categories of chronic respiratory disease. *Bull Eur Physiopath Respir* 1984;**20**:495–500.

[21] Wallwork J, Williams R, Calne R Y. Transplantation of liver heart and lungs for primary biliary cirrhosis and primary pulmonary hypertension. *Lancet* 1987;**ii**:182–5.

[22] Otulana B A, Higenbottam T W, Hutter J, Wallwork J. Close monitoring of lung function in heart-lung transplants allows detection of pulmonary rejection and infection. *Am Rev Respir Dis* 1988;**137**:245.

[23] Gray J J, Alvey B, Smith D J, Wreghitt T G. Evaluation of a commercial latex agglutination test for detecting antibodies to cytomegalovirus in organ donors and transplant recipients. *J Virol Methods* 1987;**16**:13–9.

[24] Hutter J, Scott J P, Wreghitt T G, Higenbottam T, Wallwork J. The importance of cytomegalovirus in heart-lung transplant recipients. *Chest* 1989;**95**:627–31.

[25] Brooks R G, Hofflin J M, Jamieson S W, Stinson E B, Remington J S. Infectious complications in heart-lung transplant recipients. *Am J Med* 1985;**79**:412–22.

[26] Scott J P, Higenbottam T W, Clelland C, Hutter J, Wallwork J. The natural history of obliterative bronchiolitis in patients with heart-lung transplants. *Transplant Proc* 1989;**21**:2592–3.

[27] Scott J P, Higenbottam T W. Adverse reactions and interactions of cyclosporin. *Medical Toxicology* 1988;**3**:107–27.

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Commentary

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The development of heart-lung transplantation as a new treatment for severe irreversible respiratory failure has given new hope to a large number of patients and their families facing the prospect of premature death. The extension of this procedure to the paediatric age range was inevitable and it is reassuring that the results that have been obtained from the first few cases are at least as good as those in adults. Any paediatrician who has the experience of seeing a child in terminal respiratory failure, miraculously given new life after a transplant, can only be immensely optimistic and positive about this procedure. However, it is most important that it should be put into perspective with a clear understanding of what is involved.

A practical treatment it may be for children in terminal respiratory failure. However, only a few individuals in this predicament will benefit from transplantation. From the Papworth experience so far, only 15% of referred patients have benefited.

The question that must be asked is whether the anguish of the remaining 85% is sufficiently offset by the successful outcome in the minority.

The Brompton Hospital paediatric respiratory department has assessed 18 children for transplant over the last two and half years. Only two have, so far, been transplanted. One remains well two years later and the other, after 15 months, has had a number of complications, including cytomegalovirus pneumonitis, which is currently controlled on ganciclovir and several rejection episodes culminating in the development of severe obstructive airways disease. Five children were accepted on the high priority waiting list for transplantation. Two of these patients have died and the other three are still alive. Eight referred patients were considered unsuitable for tranplantation: five for medical reasons; two who were not considered sufficiently ill to warrant transplantation; and one with major psychosocial problems who was an extremely poor complier with treatment. Amazingly the parents of three children referred for tranplant, on further reflection, did not wish their children to be included in the programme. This arose because of inadequate discussion with the family before referral. Thus my experience on smaller numbers is very similar to that at Papworth Unit, but there are additional factors to consider.

The emotional stress created by referral is enormous. Frequently it has involved travel over long distances, splitting families and creating a significant financial burden. The anguish of patients and families while waiting for transplants, in a situation when health is deteriorating rapidly, is considerable. Attitudes to impending death are fundamentally changed. Children in terminal respiratory failure must always be given appropriate treatment so that they die peacefully, with dignity, and without pain. The prospect of a transplant has sadly led to delays in institution of such treatment. This is wholly unacceptable, but the patient and parents' grim determination to struggle on as long as possible is perfectly understandable once the new hope has been generated. One of my patients who died on the waiting list, in fact indicated, a few hours before death, that she had not wanted to have a transplant. She had given her parents extra hope by acceding to their wishes. In the two weeks before death she had deliberatly stopped all her treatment and hidden it in a paper bag. A psychiatric assessment of the patient and family has, therefore, now become an essential part of the selection procedure.

Thus, in the short term, paediatricians must be aware that at best only 20% of referrals will receive a transplant, three quarters of whom can be expected to be alive after one year. At least 20% will be considered unsuitable for medical reasons, and of the remainder, half will die on the waiting list and the other half will still be waiting, perhaps a year after original referral.

At a time of medical rationing, with restriction of resources, can this procedure be justified? I believe the answer is yes, but extreme care is required before even considering referral to a centre for assessment. Only the most psychologically robust individuals, fulfilling appropriate criteria for severe respiratory failure, and without any other complicating medical problems, can be accepted on transplant programmes.

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Prognostic importance of myelosuppression during maintenance treatment of lymphoblastic leukaemia

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SUMMARY Children from the UKALL V trial were studied to assess the clinical importance of myelosuppression during uninterrupted 'maintenance' treatment of 'standard risk' lymphoblastic leukaemia. Those receiving daily 6-mercaptopurine and weekly methotrexate who were in first remission 20 months from diagnosis were divided into two groups on the basis of whether or not they had ever had an absolute neutrophil count of $<0{\cdot}5\times10^9$/l recorded during maintenance treatment up to that time. Of 105 evaluable children, 45 (43%) became neutropenic at least once, and 60 (57%) did not. Seven (16%) of the neutropenic group subsequently relapsed compared with 27 (45%) of the remainder. This difference was still significant if the analysis was stratified by total treatment time (two or three years), age, sex, or diagnostic white cell count. Seven (16%) neutropenic children died in remission, compared with one (2%) of the non-neutropenic children.

Therapeutic myelosuppression during standard maintenance treatment of 'standard risk' lymphoblastic leukaemia is associated with increased toxicity but a reduced risk of relapse. The unexplained improvement in long term survival in the United Kingdom in recent years may in large part be due to this.

Current conventional treatment of other than 'high risk' childhood lymphoblastic leukaemia includes a long phase of continuing 'maintenance' chemotherapy. This usually consists of daily 6-mercaptopurine and weekly oral methotrexate, together with occasional pulses of vincristine and prednisolone.

How important this phase of treatment is may depend on the nature and intensity of remission induction, consolidation and/or intensive 'blocks' of chemotherapy given in addition. From the observed incidence of relapse in early trials without prolonged maintenance,[1] however, and in patients who default from follow up, there can be little doubt that for many children on various regimens it is important.

Further evidence is available from UKALL V, a recent United Kingdom Medical Research Council (MRC) trial which compared three different ways of giving the same cumulative dose of 6-mercaptopurine and methotrexate in maintenance. The results were not the same, and giving 6-mercaptopurine continuously appeared to be associated with more effective disease control than intermittent dosing.[2] The basic design of a succeeding MRC trial, UKALL VIII, did not appear to differ substantially from the UKALL V 'continuous' arm, but none the less produced a sustained and striking improvement in long term disease free survival, which has yet to be explained.[3]

An impression gained by clinicians involved in UKALL VIII was of a greater incidence of treatment induced myelosuppression and morbidity during maintenance. This appeared to be due to higher cumulative doses of 6-mercaptopurine and methotrexate being given as a result of more rigidly defined prescribing criteria than in previous trials.

• Members of the Working Party during UKALL V: R M Hardisty (chairman), C C Bailey, P R H Barbor, N D Barnes, A W Craft, J M Chessells, S I Dempsey, O B Eden, P M Emerson, D I K Evans, J J Fennelly, D A G Galton, N Harker, F G H Hill, H E M Kay, D N Lawson, J S Lilleyman, T J McElwain, J R Mann, J Martin, P H Morris-Jones, M G Mott, J Peto, M Radford, M R Sandland, E N Thompson, M L N Willoughby.

If more children on UKALL VIII became neutropenic and more survived their disease, it seemed obvious to ask if the two phenomena could be related. To answer this question we chose to examine the 'continuous' arm of UKALL V. The design was very similar to UKALL VIII, but we anticipated there would be a larger proportion of patients who did not become neutropenic giving more equal group sizes for analysis. This report describes our findings.

Patients and methods

All children in the United Kingdom with 'standard risk' lymphoblastic leukaemia between the ages of 1 and 14 years, who had no meningeal disease or mediastinal mass, and who had a diagnostic white cell count <20 × 10^9/l were eligible for UKALL V. The regimen has been described in detail elsewhere,[2] but briefly consisted of remission induction with four doses of vincristine, four weeks of prednisolone, and four doses of L-asparaginase (10 000 U/m^2) after marrow recovery. This was followed by cranial irradiation, five doses of intrathecal methotrexate, daily 6-mercaptopurine (50 mg/m^2), and two further weeks of vincristine and steroid treatment before all patients were randomised to one of three continuing (maintenance) regimens. The 'continuous' arm consisted of 12 week cycles with a pulse of vincristine and steroids every six weeks, weekly oral methotrexate (20 mg/m^2), and daily 6-mercaptopurine with a target dose of 50–70 mg/m^2. the duration of treatment was randomly allocated to two or three years. Co-trimoxazole was not given as part of the protocol.

The trial opened in January 1976 and closed in March 1979, accruing 528 patients. The record cards for all children who remitted, who did not relapse before the completion of six cycles (18 months) of maintenance treatment, and who received the 'continuous' arm were reviewed. Every recorded neutrophil count from the start of randomised treatment was extracted and entered into a computer file containing other patient details including treatment outcome.

Patients were divided into two groups simply on the basis of whether they had ever had a recorded neutrophil count below 0·5 × 10^9/l or not. The two groups so defined were compared for any difference in treatment related mortality and recurrence of disease using the log rank method with two tailed p values, and simple 2 × 2 χ^2 tests with Yates's correction.

Results

Four hundred and ninety six patients remitted on UKALL V, of whom 161 were allocated to the 'continuous' arm of treatment. One hundred and five completed their first six cycles of treatment every three months in remission and had their neutrophil counts examined. They form the basis of the present study.

Of the 105, 60 (57%) never produced a neutrophil count below 0·5 × 10^9/l whereas 45 (43%) did so on at least one occasion. With a minimum follow up time of eight and a half years, seven (16%) of the neutropenic children have relapsed compared with 27 (45%) of the others (see figure). This difference is significant (2×p=0·002; log rank), and remains so if the duration of remission is stratified by age (<3, 3–8, >8 years: 2×p=0·004), diagnostic white cell count (<10, >10 × 10^9/l: 2×p=0·002), sex (2×p=0·003), or all three (2×p=0·05). In the 'continuous' arm of UKALL V there was a significant excess of marrow relapses in those randomised to two years rather than three years treatment (p=0·02, as described elsewhere[2]), but even if the neutropenic and non-neutropenic groups are stratified for this variable, the difference in relapse rate remains significant (2×p=0·02). The proportions of the two groups in the age, sex, white cell count, and treatment categories is shown in the table.

Of the 105, eight (8%) died in remission: seven from the neutropenic group (16%) and one of the others (2%). The excess of remission deaths in the neutropenic group is significant (χ^2=5·2; p<0·05). The treatment related mortality pattern makes the difference in eight year event free survival (as opposed to remission duration) between the neutropenic (69%) and non-neutropenic (53%) groups no longer significant (2×p=0·11), though the trend remains.

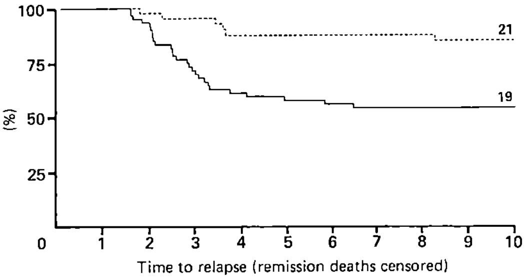

Figure *Duration of remission for 105 children on UKALL V 'continuous'. Time scale in years from diagnosis; (– – –) 45 who had a neutrophil count <0·5 × 10^9/l during the first 18 months of maintenance treatment on at least one occasion; (——) 60 who never had a neutrophil count <0·5 × 10^9/l during the same period. Log rank: 2×p=0·002.*

Table *UKALL V 'continuous' regimen*

Neutrophil count during weeks 11–96	*Total*	*Boys*	*Girls*	*Diagnostic white cell count*		*Age (years)*			*Treatment (years)**	
				>10 × 10^9/l	*<10 × 10^9/l*	*<3*	*3–8*	*8+*	*2*	*3*
Patients who had count $<0{\cdot}5\times10^9$/l:										
At least once	45	18	27	11	34	12	29	4	18	17
Never	60	31	29	13	47	9	41	10	20	24
Total	105	49	56	24	81	21	70	14	38	41

*Several of the 105 patients relapsed before this randomisation occurred.

The timing of neutropenia did not seem important in terms of whether it occurred within the first nine months of treatment or later, nor did the frequency of neutropenic episodes in terms of the number of recorded neutrophil counts $<0{\cdot}5 \times 10^9$/l provided it was less than three. Children who had profound neutropenia on more than four occasions (there were only four so the numbers are very small) may paradoxically have a higher relapse rate. Two relapsed, and comparison with those who became neutropenic one, two, or three times gives $2\times p=0{\cdot}01$; the observed:expected ratio was 2·7.

The method of defining neutropenia did seem important, and no difference in the relapse rate of the 105 could be seen if the patients were divided around a threshold neutrophil count of $1{\cdot}0 \times 10^9$/l, or if a median value for each patient was calculated.

Discussion

The clear implication from this cohort study is that treatment induced myelosuppression during continuing (maintenance) therapy for standard risk lymphoblastic leukaemia is associated with greater toxicity but better disease control. Most of the episodes of neutropenia observed would have been due to chemotherapy as another major myelosuppressant, co-trimoxazole, was not used in UKALL V.

The findings support the hypothesis that much of the improvement in long term survival seen in the United Kingdom after 1980 is due to increased cytotoxicity of 6-mercaptopurine and methotrexate maintenance treatment. Before that time, although the protocol design and doses were similar, clinicians had no guidelines on dose adjustment in the face of neutropenia or thrombocytopenia and many tended to use amounts which avoided profoundly low counts, as can be seen from the high proportion of children (57%) in our study cohort who never had a neutrophil count below $0{\cdot}5 \times 10^9$/l during the first 18 months treatment. The incidence of neutropenia in UKALL VIII is still being analysed, but it would appear to be higher.

Surprisingly few studies have looked at this aspect of maintenance chemotherapy before, though 18 years ago Pinkel *et al* showed that halving the drug doses shortened remission and reduced long term survival rates.[4] Van Eys *et al,* for the Pediatric Oncology Group, prospectively studied 430 children with good risk lymphoblastic leukaemia who were randomly assigned to continuing treatment designed to maintain a total white cell count of either (a) 1·5–3·0 or (b) 3·0–5·0 × 10^9/l and found no difference in disease free survival, though the children in group (a) appeared to suffer more serious infections.[5] Superficially this would appear to contradict our findings, but two points should be stressed about the Pediatric Oncology Group study. Firstly, the overall results, like UKALL V, were not good for either (a) or (b) by current standards (five year disease free survival of <50% for good risk lymphoblastic leukaemia) and secondly, part of the protocol for both groups was to keep the neutrophil count well above $0{\cdot}5 \times 10^9$/l. It is possible that patients in both arms of the study from the Pediatric Oncology Group received inadvertent inadequate treatment in much the same way as the non-neutropenic patients in UKALL V. More recently Schmiegelow *et al* found that the mean white cell count during maintenance treatment was a prognostic factor second only in importance to the diagnostic white cell count in a group of 84 Nordic children.[6] Despite different methods of analysis (the mean white cell count and minimum neutrophil count measure different things) their patients were similar and the Scandinavian findings and conclusions broadly agree with our own.

The practical point is that 'classical' maintenance treatment can probably be made more effective in terms of disease control if the doses of 6-mercaptopurine and methotrexate are pushed to the point where occasional neutrophil counts $<0{\cdot}5 \times 10^9$/l are produced. This has been standard practice for years in some centres,[7] but is by no means always the case. In many patients it may have been achieved fortuitously in UKALL VIII, and this would explain the improved results. The greater treatment induced morbidity and mortality that pushing treatment to toxicity undoubtedly produces may be alleviated by improved supportive treatment, and may be a price worth paying anyway in terms of overall long survival. Frequent neutropenia may paradoxically have the opposite effect if it leads to prolonged interruption of treatment, but this is a data derived hypothesis that needs confirmation from other studies.

Ideally, the suggestion that therapeutic myelosuppression can reduce the relapse rate in lymphoblastic leukaemia should be subjected to further clinical trial, but such a trial would be extremely difficult to structure, would require a degree of physician compliance unlikely to be achieved, and would be ethically questionable as it would be based on demonstrating an inferior result for half of the entrants. In the face of evidence already available it would seem reasonable to adopt the practice at this stage in all future regimens.

References

[1] Preliminary Report to the Medical Research Council by the Leukaemia Committee and the Working Party on Leukaemia in Childhood. Treatment of acute lymphoblastic leukaemia. Comparison of immunotherapy (BCG), intermittent methotrexate and no therapy after a five-month intensive cytotoxic regimen (Concord trial). *Br Med J* 1971;**iv**:189–94.

[2] Report to the Council by the Working Party on Leukaemia in Childhood. Medical Research Council Leukaemia Trial—UKALL V: an attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic leukemia. *J Clin Oncol* 1986;**4**:1758–64.

[3] Report to the Council by the Working Party on Leukaemia in Childhood. Improvement in treatment for children with acute lymphoblastic leukaemia. The Medical Research Council UKALL Trials, 1972–84. *Lancet* 1986;**i**:408–10.

[4] Pinkel D, Hernandez K, Borella L, *et al.* Drug dosage and remission duration in childhood lymphocytic leukemia. *Cancer* 1971;**27**:247–56.

[5] Van Eys J, Chen TT, Berry D, *et al.* The effect of drug dosage on outcome and infectious complications in the treatment of childhood lymphocytic leukemia. *Proceedings of the American Society for Clinical Oncology* 1981;**22**:478.

[6] Schmiegelow K, Pulczynska MK, Siep M. White cell count during maintenance chemotherapy for standard-risk childhood acute lymphoblastic leukemia: relation to relapse rate. *Pediatric Hematology and Oncology* 1988;**5**:259–67.

[7] Pinkel D. 6-Mercaptopurine dosage. *Lancet* 1987;**ii**:1267.

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Monitoring treatment in congenital adrenal hyperplasia

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SUMMARY We report results of monitoring treatment in 41 patients with congenital adrenal hyperplasia controlled over 0·3–13·1 years using standard auxological techniques alone. Doses of glucocorticoid (15–25 mg/m^2/day) and mineralocorticoid (0·15 mg/m^2/day) replacement were determined initially using biochemical indices and thereafter adjusted according to surface area. Monitoring was solely directed at maintaining a 50th centile height velocity for chronological age. Of 41 patients, 32 were referred after the newborn period. Nearly half of these patients were either overtreated or undertreated before their referral. Of the nine treated from birth, all but one were in good control and only two have had a second hospital admission. Present height standard deviation scores (SDS) for chronological age range from −1·60 to −0·26. Height SDS for bone age were compared with midparental heights in 33 patients: 15 treated with early emphasis on growth had a height prognosis exceeding midparental values; patients who had experienced appreciable prior overtreatment or undertreatment fared less well. In the long term management of congenital adrenal hyperplasia correction of salt loss is of prime importance. Doses of glucocorticoid required in addition to mineralcorticoid replacement should be continuously assessed and adjusted to maintain a normal growth velocity. This is most conveniently achieved by standardising replacement doses on surface area.

The object of treatment in congenital adrenal hyperplasia is to maintain normal health and growth by glucocorticoid and mineralocorticoid replacement, which has the effect of suppressing adrenal production of androgens and their precursors. Overtreatment or undertreatment with cortisol or fludrocortisone is detrimental in all respects but especially to growth, and strict monitoring of steroid profiles in conjunction with clinical indices has been recommended.[1] The pursuit of normal biochemical indices of control has been disappointing in terms of outcome.[2] This is probably attributable to episodic fluctuations in the secretion of steroids. We propose that the use of standard auxological techniques alone is a simple, effective, and painless method of monitoring control, and we have studied the growth of 41 patients with congenital adrenal hyperplasia who were monitored in this manner over 13 years.

Patients and methods

Forty one patients (22 boys, 19 girls) with congenital adrenal hyperplasia (21-hydroxylase deficiency) who had been followed up in the endocrine clinic were studied. Diagnosis was based on detailed endocrine investigations. All patients initially had raised serum 17-OH progesterone, androgen, and adrenocorticotrophic hormone concentrations and abnormal 24 hour urinary steroid excretion. A salt losing state was confirmed by the presence of hyponatraemia, hyperkalaemia, and raised plasma renin activity with low serum aldosterone concentration. Doses of replacement steroids were initially individually established while the diagnosis was being made or confirmed after referral using biochemical indices and thenceforward adjusted according to surface area to ensure the maintenance of normal growth velocity, which was taken as evidence of good control.

The patients were followed up every three months for the first one to two years of life and every six months thereafter. At all visits standard auxological assessment was performed.[3] Blood pressure was monitored in all salt losing patients on fludrocortisone replacement. Bone age assessment was performed at yearly or two yearly intervals after the age of 2 years by the Tanner-Whitehouse method.[4] No biochemical monitoring was done after the initial investigations.

All growth measurements in this study have been expressed as a standard deviation score (SDS) for chronological age and bone age. A score was calculated from the formula[5] $\text{SDS}=(X-\bar{X})\ S$ where X is the measurement in the individual and $\bar{X}$ and S are the mean and standard deviation respectively for the general population.[6] The midparental height adjusted for sex was taken as the target height and this was also expressed as a SDS.

Patients received treatment with oral hydrocortisone 15–25 mg/m^2/day in two or three divided doses; prednisolone 4 mg/m^2/day was used in some patients with problems of hypoglycaemia. Fludrocortisone (0·15 mg/m^2/day) was given to salt losing patients in addition. In infancy, a higher dose of fludrocortisone (up to 0·25 mg/m^2/day) was used on occasion in addition to salt supplementation.

The height SDS for chronological age and bone age at the time of presentation to the clinic were compared with present values. Wilcoxon matched pairs signed rank test was used to compare these

Table *Clinical profile and growth data on patients with congenital adrenal hyperplasia*

Patient No	*Sex*	*Salt loser*	*Age at diagnosis*	*Age at referral to clinic*	*Follow up (years)*	*Height SDS for chronological age*		*Height SDS for bone age*		*Midparental height SDS*	*Comments*
						At referral	*At present*	*At referral*	*At present*		
1	M	+	0·05	0·98	13·12	−3·08	−0·07	−3·88	−0·86	−1·26	Overtreated*
2	F	+	0·03	0·30	3·60	−2·50	−0·58	—	+0·91	+0·63	Overtreated*
3	F	+	0·03	0·30	2·09	−1·27	−1·60	—	+1·54	+1·39	Overtreated*
4	F	+	0·02	3·21	7·60	−2·00	−2·10	—	+1·34	−0·20	Overtreated*
5	M	+	0·03	2·24	3·06	−2·18	−0·75	−1·63	+0·66	−0·82	Overtreated*
6	M	+	0·03	8·35	7·65	−1·06	−1·97	+0·88	−2·36	−1·63	Overtreated*
7	M	+	0·03	10·90	6·90	−2·32	−3·34	−2·00	−3·34	−1·63	Overtreated*
8	M	+	0·04	1·50	0·30	−2·49	−2·10	—	—	−1·83	Overtreated*
9	F	+	0·03	16·23	1·60	−2·73	−2·58	−2·23	−2·58	−1·00	Undertreated*
10	F	+	0·02	5·40	5·60	+0·69	−0·60	−1·54	−1·10	+0·40	Undertreated*
11	M	+	0·05	7·73	2·83	+1·76	+0·60	−0·56	−0·63	+0·63	Undertreated*
12	M	+	0·10	9·30	4·90	+0·48	+0·42	−0·86	−0·22	+1·36	Undertreated*
13	M	+	0·04	5·50	6·20	+1·01	−0·30	−2·52	−2·14	−0·85	Undertreated*
14	F	+	0·03	12·00	6·26	+0·88	−0·70	−0·93	−0·70	+0·46	Undertreated*
15	M	+	0·03	14·60	8·20	−1·00	−2·00	−2·37	−2·00	+0·04	Undertreated*
16	M	+	0·04	6·63	4·91	−2·84	−1·79	+0·37	+0·32	−0·51	Associated partial growth hormone insufficiency
17	F	+	0·04	0·20	6·10	−1·07	−1·70	—	+1·00	+0·65	Associated partial growth hormone insufficiency
18	F	−	8·00	8·00	0·60	+1·96	+2·00	−1·60	—	+1·05	Virilisation
19	M	−	9·00	9·00	6·30	+2·39	−0·97	−2·45	−2·20	−1·15	Precocious puberty
20	M	−	7·15	12·60	2·40	+2·60	+0·63	−0·50	−0·34	+1·53	Precocious puberty
21	M	+	0·04	4·00	2·00	−0·48	−1·28	—	−1·90	−0·85	Poor compliance
22	M	+	0·04	0·44	6·67	−0·43	−0·27	−1·50	−2·30	−0·40	Poor compliance
23	M	+	0·08	2·14	1·80	−1·75	−1·30	—	−2·50	−0·40	Poor compliance
24	F	+	0·02	1·73	4·70	−0·12	0·00	−0·09	+2·80	—	Adopted child
25	M	+	0·02	3·50	5·60	−0·54	+0·25	+0·41	+0·50	+0·40	
26	F	+	0·05	0·60	4·23	−1·70	−1·13	—	+1·30	+0·63	
27	M	+	0·10	0·40	0·63	−1·10	−1·48	—	—	−0·93	
28	F	+	0·02	0·20	1·75	−0·20	−0·33	—	+1·49	+0·53	
29	F	+	0·04	1·00	3·38	−0·60	−0·66	−0·90	−0·18	−1·26	
30	F	+	0·05	7·50	9·30	−0·57	−0·30	−0·79	−0·30	−0·20	
31	F	+	0·03	0·82	2·60	−0·57	+0·96	—	+3·08	+0·97	
32	F	+	0·02	0·24	4·26	−0·32	+1·46	+0·28	−0·40	−0·20	
33	F	−	0·12	0·12	5·91	+0·88	+1·28	+1·80	−0·60	+0·35	Poor compliance
34	F	+	0·03	0·03	6·31	−2·08	−1·33	−1·59	+0·95	−0·24	Low birth weight
35	M	+	0·02	0·02	3·81	−2·00	−0·16	—	+0·34	+0·39	Low birth weight
36	F	+	0·02	0·10	3·20	−3·26	−1·60	—	+0·20	−1·00	Low birth weight
37	M	+	0·15	0·15	10·35	−2·03	−1·47	+1·76	+1·15	—	Adopted child
38	F	+	0·03	0·11	4·39	+1·53	−0·26	+3·03	+2·50	−0·48	
39	M	+	0·10	0·10	1·40	−1·99	−0·83	—	−0·83	−0·60	
40	M	+	0·03	0·18	9·97	−2·50	−1·31	−1·06	+0·20	+0·50	
41	M	+	0·04	0·10	0·50	−0·50	−0·80	—	—	+0·40	

*Overtreated or undertreated till time of referral.

paired sets of data. The height SDS for bone age at present was compared with the midparental height SDS using the line of identity between the two.[5]

Results

The clinical data of the patients are shown in the table. All had 21 hydroxylase deficiency and all but four were salt losers. The present age ranged from 0·6 to 22·8 years. Nine patients had completed puberty and five had attained final height.

Of 41 patients, 32 (patients 1–32) were referred after the newborn period and nine (patients 33–41) were treated from birth in our department.

Of the patients referred, eight had been overtreated with high doses of steroids and had growth retardation, cushingoid features, and delayed bone age and seven had been undertreated with low doses of steroids and had sexual precocity and advanced bone age at the time of referral. Two others have been found to have partial growth hormone insufficiency during follow up and have been treated additionally with daily subcutaneous growth hormone. Three of the non-salt losers presented between 7 and 9 years of age with either signs of virilisation or precocious puberty and advanced bone age. Compliance was poor in three patients. The remaining nine patients were in good control as reflected by their normal growth.

Of those who were treated from birth, only one patient was non-compliant and had advanced bone age. The rest were in good control and only two of these patients required a further admission to hospital after the initial diagnosis had been established and treatment instituted. Present height SDS for chronological age ranged from −1·60 to −0·26 and for all those in whom bone age data were available, prognosis of final height was good.

Height SDS for chronological age at time of presentation to this hospital and values at present are shown in fig 1a. Height SDS for bone age are compared in a similar way in fig 1b. There were no significant changes between any of the values. In other words, the treatment regimen had been successful in maintaining normal growth from the time of its institution.

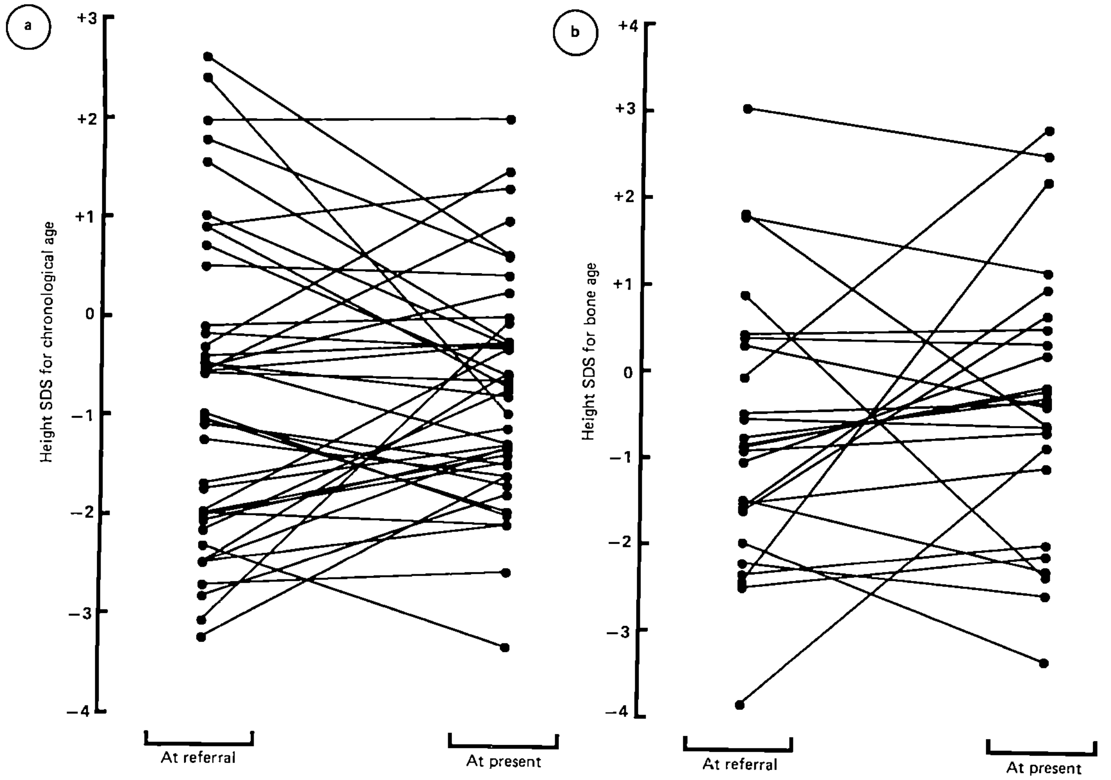

Fig 1 *(a) Height SDS for chronological age at referral and at present; (b) height SDS for bone age at referral and at present.*

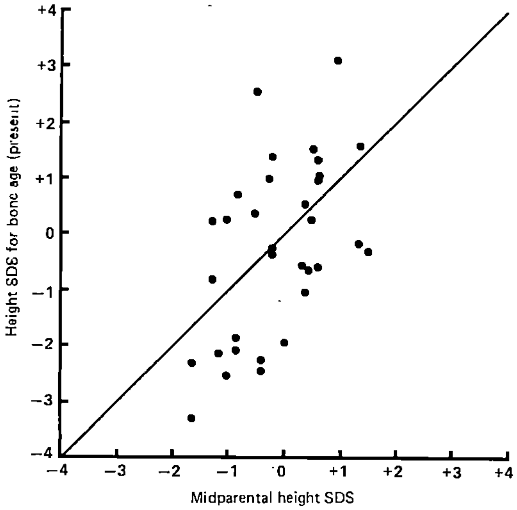

Fig 2 *Comparison of height SDS for bone age at present with midparental height SDS.*

Fig 2 shows the association between height SDS for bone age at present and the midparental height (target height) SDS. Of 33 sets of values available, 18 were either above or close to the line and 15 below the line. The 18 patients whose values lay above or close to the line were those treated with early emphasis on growth management. Five of these 18 were overtreated from one to three years of life before referral. One patient has already achieved a final height appropriate to target height. The remaining 17 patients will probably attain a final height at or above the target height if they remain in good control. Of the 15 whose values were below the line, four patients had attained final heights below midparental heights; they belonged to the categories of either overtreatment for a prolonged period or undertreatment with late referral. The remaining 11 patients will probably attain a final height below the target height. Of these, four were patients who were undertreated and had advanced bone age at the time of referral, one was overtreated for eight years and had growth retardation at the time of referral, two were late diagnosed congenital adrenal hyperplasia with advanced bone age, and four had poor compliance.

Discussion

The aims of management in congenital adrenal hyperplasia are to maintain normal health, to suppress the effects of excessive androgen secretion, to maintain a normal growth velocity, to undergo normal puberty, and to achieve a final height as close to target height as possible. Undersuppression of adrenocorticotrophic hormone leads to increased height velocity and advanced bone age; oversuppression leads to the reverse and the recommended replacement dose of cortisol in congenital adrenal hyperplasia for optimal growth effects is 20–25 mg/m^2/day.[7] There is surprisingly little individual variation but there is a differing effect of treatment with glucocorticoids between patients.[8] In salt losers, adequate replacement with fludrocortisone and salt in the newborn period is crucially important for maintenance of good health and optimal control because insufficient mineralocorticoid treatment results in hypovolaemia, hyponatraemia, hyperkalaemia, and a raised plasma renin activity, which leads to loss of glucocorticoid control.[9] It is often not appreciated, however, that fludrocortisone not only exerts mineralocorticoid effects but also has appreciable glucocorticoid effects.[10] The dosage of fludrocortisone should be matched to surface area and the glucocorticoid contribution must be remembered before an increase in the dose of cortisol is instituted. At puberty, the rise in sex steroid secretion, increased growth velocity, and rapidly changing surface area require appropriate parallel increases in glucocorticoid and mineralocorticoid dosages to prevent loss of androgen control and consequent rapid acceleration in bone age.

As the object of treatment is to suppress adrenocorticotrophic hormone drive and not simply to replace cortisol and flurocortisone, the ideal method for assessing individual dose should be to titrate the concentration of glucocorticoid against the adrenocorticotrophic hormone concentration and mineralocorticoid against plasma renin activity.[11] In practice, however, interpretation of the adrenocorticotrophic hormone concentration is difficult because of the circadian variation and measurement of plasma renin activity is affected by diet and postural factors.[12] Monitoring by single random plasma measurements of 17-OH progesterone has been shown to be unreliable as an index of therapeutic control with glucocorticoids as there is a pronounced circadian rhythm.[13 14] With episodic fluctuations in the secretion of the steroid and the timing of sample collection with respect to the last dose of cortisol, there is great difficulty in the interpretation of the values. Serial measurements of 17-OH progesterone in plasma, capillary blood, and saliva have been used to assess control and nomograms have been employed to interpret the daily profiles.[15 16]

The disadvantages of monitoring by biochemical steroid indices are manifold. Such studies measure adequacy of control over a short period of time only. As serial sampling of saliva and capillary blood is usually undertaken at home, the validity of the technique is dependent on the reliability of the patient. Anticipation of sampling might also lead to good short term compliance with medication, which may not necessarily apply to the long term results. Infrequent sampling gives erroneous results because of the circadian rhythm and fluctuation in the secretion of steroids.

Obsession to achieve biochemical perfection often over-rides the realisation of the importance of accurate measurements of stature and assessment of growth velocity and skeletal maturity. Attempts to achieve 17-OH progesterone concentrations within the range for normal individuals by increasing or decreasing the dose of cortisol leads to oscillations between overtreatment and undertreatment, both of which are deleterious to growth.[7] From our data, it can be seen that this was a frequent error in the management of congenital adrenal hyperplasia, but overtreatment during the infantile component of growth is probably less hazardous in compromising height prognosis, provided the situation is rectified over the course of the childhood component of growth.[17] Undertreatment, on the other hand, almost always compromises final height because an advanced bone age can rarely be recovered.

Results from the study of congenital adrenal hyperplasia by Winter and Couch showed the median height to be the 25th centile.[1] Thus as a group, these patients were generally shorter than their peers. This has also been the experience in the study by DiMartino-Nardi *et al.*[2] In both of these studies, monitoring was by frequent assessments of serum 17-OH progesterone, testosterone, and plasma renin activity but more emphasis was placed on these than on growth velocity. We submit that if the desired end result is normal growth the best method of monitoring treatment is to concentrate on this rather than on biochemical indices. This requires particularly close follow up during periods of rapid growth in infancy and puberty and frequent adjustment of medication at such times.

References

[1] Winter JSD, Couch RM. Modern medical therapy of congenital adrenal hyperplasia. *Ann NY Acad Sci* 1985;**458**:165–73.

[2] DiMartino-Nardi J, Stoner E, O'Connell A, New MI. The effect of treatment of final height in classical congenital adrenal hyperplasia. *Acta Endocrinol [Suppl] (Copenh)* 1986;**279**: 305–14.

[3] Brook CGD. *Growth assessment in childhood and adolescence.* Oxford: Blackwell Scientific Publications, 1982.

[4] Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H. *Assessment of skeletal maturation and prediction of adult height (TW2 method).* New York: Academic Press, 1983.

[5] Snedecor GW, Cochran WG. *Statistical methods.* 6th ed. Iowa City: Iowa State University Press, 1967.

[6] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. Part II. *Arch Dis Child* 1966;**41**:613–35.

[7] Brook CGD, Zachmann M, Prader A, Murset G. Experience with long term therapy in congenital adrenal hyperplasia. *J Pediatr* 1974;**85**:12–9.

[8] Hansen JW, Loriaux DL. Variable efficacy of glucocorticoids in congenital adrenal hyperplasia. *Pediatrics* 1976;**57**:942–7.

[9] Rösler A, Levine LS, Schneider B, Novogroder M, New MI. The interrelationship of sodium balance, plasma renin activity and ACTH in congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1977;**45**:500–12.

[10] Forest MG. Adrenal steroid deficiency states. In: Brook CGD, ed. *Clinical paediatric endocrinology.* 2nd ed. Oxford: Blackwell, 1989:384.

[11] Brook CGD. Congenital adrenal hyperplasia. Pathology, diagnosis and treatment. In: James VHT, ed. *The adrenal gland.* New York: Raven Press, 1979:243–57.

[12] Oparil S. Theoretical approaches to estimation of plasma renin activity: a review and some original observations. *Clin Chem* 1976;**22**:583–93.

[13] Atherden SM, Barnes ND, Grant DB. Circadian variation in plasma 17-hydroxyprogesterone in patients with congenital adrenal hyperplasia. *Arch Dis Child* 1972;**47**:602–4.

[14] Frisch H, Parth K, Schober E, Swoboda W. Circadian patterns of plasma cortisol, 17 hydroxyprogesterone and testosterone in congenital adrenal hyperplasia. *Arch Dis Child* 1981;**56**:208–13.

[15] Hughes IA, Dyas J, Robinson J, Walker RF, Fahmy DR. Use of serial measurements of 17-OH-progesterone in plasma, capillary blood and saliva. *Ann NY Acad Sci* 1985;**458**:193–202.

[16] Young MC, Robinson JH, Read GF, Riad-Fahmy D, Hughes IA. 17 OH-progesterone rhythms in congenital adrenal hyperplasia. *Arch Dis Child* 1988;**63**:617–23.

[17] Karlberg J, Engstrom I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model. *Acta Paediatr Scand* 1987;**76**:478–88.

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Teenage sexuality: implications for controlling AIDS

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SUMMARY A study on 761 teenagers aged 15–17 years showed that 56% of both sexes had had a steady or serious relationship. For about 40% of both sexes intercourse was a part of this relationship. Teenagers know how AIDS is transmitted, but only one third indicated personal concern about the epidemic. Only a fifth anticipate a single monogamous relationship. Significantly more girls than boys are planning to have fewer partners. Of these not anticipating monogamy three quarters mentioned the use of condoms. If education is to be effective in reducing the AIDS epidemic it must be sufficiently relevant to create and maintain changes in life style and must also educate teenagers before they have established patterns of behaviour.

A major way in which the impact of the AIDS epidemic could be reduced is by public education and individual risk reduction. If education is to be effective it must begin in the teenage years before patterns of sexual behaviour have been established. There are few published data on the effect of the government AIDS campaign on the teenage population who are potentially the generation most at risk from the epidemic.

This study was undertaken as an extension of our previous study of teenage pregnancy in east Devon.[1] Between March and October 1987 we surveyed teenagers aged between 15 and 17 years, from seven schools in a semirural area, to determine how they viewed the development of teenage relationships, to establish the extent of sexual experience, and to assess their knowledge of AIDS.

Subjects and methods

The seven schools were selected to ensure adequate size groups for statistical analysis of city and rural populations, of the intellectually able, and of social class I and II. They included three coeducational comprehensives, two single sex private schools, a sixth form college, and the last grammar school year (lower sixth) of a school recently made comprehensive; all were approached via the headmaster or principal, in the first instance by letter and then by a visit to explain the nature of the research. Consent was obtained from the parents of the fourth and fifth formers. The study was approved by the district research ethics committee.

The teenagers were seen either in class or year groups. The same format was used each time a school was visited. A doctor, introduced by a teacher, spoke for 5–10 minutes about the study and its aim to find out about the development of relationships, making clear we were aware that some teenagers would be sexually active. Emphasis was placed on the complete confidentiality of the questionnaire, the necessity for serious consideration of the questions, and accuracy for the sake of the research. The need for us to have a record of their own view rather than what they expected *we* would like or they *'should'* say was stressed.

All members of the year groups selected by the researchers were present for the introduction; in no case was parental consent withheld. The teenagers were encouraged to create their own personal space in which to answer. They were told that they need not complete it if they did not wish to. Seven hundred and sixty one questionnaires were completed; four were returned blank or incomplete and these were take to represent refusals. One hundred and forty two (19%) of the teenagers who had completed the questionnaire were asked to discuss their questionnaire confidentially with one of the researchers; one refused. This check allowed verification that the questions had been understood correctly.

We were able to determine from the questionnaire whether any individual was sexually experienced using data on their most serious relationship, their knowledge of the 'normal' progression for their friends at each stage of a relationship, and whether the teenager agreed with that progression for themselves. The sexual activity of each teenager whose questionnaire was verified was checked verbally and compared with the data derived from the questionnaire. A number of teenagers did not answer all the questions.

Results

Fifty six per cent of both sexes (175/311 boys and 212/374 girls) had had a relationship that they regarded as steady or more serious, a quarter a less serious friendship, and just under a fifth had never had a girl or boyfriend (50/311 boys and 53/374 girls).

The perception of *their friends'* relationships was used to explore the development of teenage relationships and the prevalence of full sexual activity. The figure shows how the girls expected a relationship among their friends to progress with a fifth expecting no physical involvement on their first date, although most expected to be kissing. By the fourth date virtually all expected kissing and a third petting. By the time the relationship was regarded as steady half expected their friends to be having intercourse and over 90% to be having intercourse when the relationship was serious.

The pattern for the boys was not significantly different and again half expected their friends to be having intercourse when the relationship was steady.

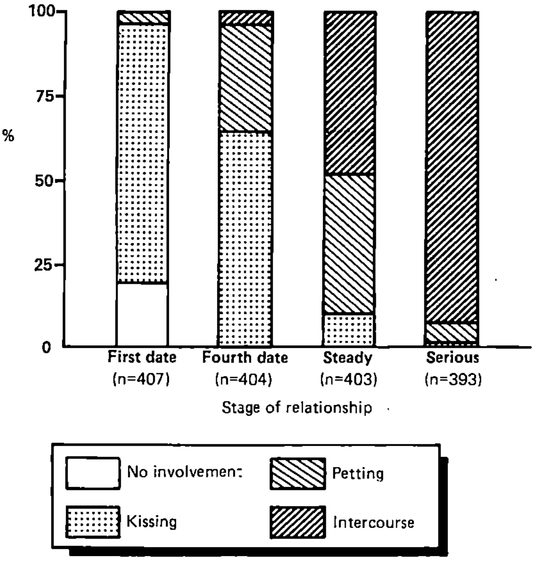

Figure *Expected progression of relationship among female friends.*

It was important to define what the teenagers meant by 'steady'. Over half of the boys and just under half of the girls said that a steady relationship would be established within two months of going out with the same person. Less than a tenth gave a time of greater than six months. The median time was eight weeks for boys and 10 weeks for girls (table 1).

Using the derived estimate of sexual intercourse a fifth of the total population of 15 year olds were sexually experienced as were a quarter of 16 and 17 year olds (table 2). When only those who have had a steady or serious relationship are considered, this figure is almost doubled for girls at all ages, and for the boys the numbers increased from a third at 15 years to about half at 17 years.

A variation in the number who were fully sexually active was noted between schools with 34% of fifth form girls and 21% of fifth form boys at one coeducational comprehensive school being experienced in contrast with 18% and 14% respectively at another coeducational comprehensive school (table 3).

A grouping effect was noted between friends with significantly more of those who were sexually active

Table 1 *Teenagers' definition of a steady relationship*

Minimum period of relationship (months)	*No (%) girls*	*No (%) boys*
	(n=324)	*(n=258)*
1–2	138 (43)	150 (58)*
3–4	113 (35)	69 (27)
5–6	44 (14)	22 (9)
>6	29 (9)	17 (7)
Median (weeks)	10	8

*Significant difference (p<0·001).

Table 2 *No (%) of teenagers who have had intercourse*

	Age (years)		
	15	*16*	*17*
Girls:			
From the whole group	40/208 (19)	38/152 (25)	13/57 (23)
Of those with a steady or serious relationship	40/100 (40)	37/79 (47)	13/32 (41)
Boys:			
From the whole group	25/157 (16)	23/99 (23)	22/87 (25)
Of those with a steady or serious relationship	22/71 (31)	22/56 (39)	22/48 (46)

having friends who were also experienced; this was true for both sexes.

The teenagers were asked to indicate how many of their friends *said* they were sexually experienced and how many they *thought* were experienced. The results from both questions were similar, table 4 showing what friends 'said'. The boys' estimates of the numbers of either their male or female friends who were sexually active and the girls' estimates of their female friends activity broadly corresponded to the estimate of sexual activity derived from the data (table 2), but girls gave significantly higher estimates of the number of male friends who they thought were or said they were having intercourse. There was a trend for more of the older teenagers of either sex to be sexually experienced. The increase of sexual experience with age was related to the number who had had a steady or more serious relationship with the amount of sexual activity within such relationships being similar at 15 and 17 years for girls and increasing from a third to a half for the boys.

There was no significant difference by age and sexual activity and career plans for either sex except that for the 15 year old girls where significantly more of those who were planning to go on to higher education were virgins ($p<0{\cdot}05$).

The sexually experienced girls were more likely to have started their periods before 12 years of age than those who were still virgins ($p<0{\cdot}001$) (35/85 compared with 37/301).

The boys had less supervision by parents than the girls. There was no difference in parental supervision for the boys who were sexually experienced except that more parents of boys who were virgins stayed awake until they were home ($p<0{\cdot}05$). In contrast the girls who were sexually experienced had significantly less supervision in terms of permission to go out, time to be home by, parents staying awake, and parents knowing where their daughters were ($p<0{\cdot}01$). For the boys there was no significant difference between sexual activity and the social class of the family (using the Registrar General's classification of father's occupation) (table 5), but the girls from the non-manual sector (I–IIIn) were significantly less likely to be sexually active than those from social class IIIm–V.

The teenagers were asked to state in their own words what they thought AIDS was (table 6). Significantly more of the 17 year olds (that is, sixth formers) wrote down what the initials stood for and that it affected the immune system. However, significantly more of the 15 year olds than the 17 year olds stated it was sexually transmitted. A quarter at all ages wrote down that there was no cure.

Significantly more of the girls than the boys were personally worried about AIDS but only 36% of girls and 30% of the boys felt that AIDS might affect them personally and were therefore concerned about it as a risk. The teenagers were asked to state what precautions they would take against contracting AIDS. A fifth of girls and less than a fifth of boys planned to have a single monogamous relationship (table 7). Of those who did not state this 75% of the girls and just under 70% of the boys mentioned the use of condoms. Significantly more girls than boys said they would want to know their partner well

Table 3 *Variation in sexual activity between teenagers at different schools*

School and year group	*No (%) girls*	*No (%) boys*
Fourth form (age 15):		
Private	4/39 (10)	
Fifth form (age 16):		
Comprehensive 1	24/70 (34)	13/61 (21)
Comprehensive 2	13/47 (28)	11/50 (22)
Comprehensive 3	16/88 (18)	14/100 (14)
Private	9/65 (14)	
Sixth form (age 17):		
Comprehensive 3	8/43 (19)	4/32 (13)
Private	4/11 (36)	14/59 (24)
Grammar	1/9 (11)	8/21 (38)
College	12/45 (27)	6/21 (29)

Table 4 *Perception of friends' sexual activity by both those who are and are not sexually active themselves*

	No (%) girls	*No (%) boys*
At least half *male* friends experienced:		
Virgins	70/218 (32)	28/206 (13)
Sexually active	54/74 (73)	23/57 (40)
At least half *female* friends experienced:		
Virgins	54/282 (19)	35/152 (23)
Sexually active	44/75 (59)	30/56 (54)

Table 5 *Sexual activity and social class*

	No (%) girls	*No (%) boys*
Class:		
I–II	31/190 (16)	29/150 (19)
III non-manual	7/47 (15)	13/39 (33)
III manual	29/87 (33)	13/59 (22)
IV–V	8/18 (44)	3/21 (14)

Table 6 *Replies to the question (by age group)—What is AIDS?*

	Girls			*Boys*		
	≤15 (n=189)	*16 (n=148)*	*≥17 (n=55)*	*≤15 (n=132)*	*16 (n=82)*	*≥17 (n=82)*
% Who stated that it was:						
Acquired immune deficiency syndrome	16	31	40	23	33	54
Virus	15	19	18	10	11	24
Sexually transmitted disease	61	40	40	56	38	29
Associated with drugs/needles	7	7	13	9	5	1
Affected immune system	22	39	44	26	37	59
Associated with secondary infection	12	14	9	7	11	28
Associated with homosexuals	4	5	5	5	4	2
Incurable	27	26	20	22	24	23

Table 7 *Precautions the teenagers would take against AIDS*

	No (%) girls	*No (%) boys*
All teenagers:	(n=417)	(n=344)
Would not use drugs/ care with needles	89 21	55 17
Monogamous relationships	87 21	56 16
Of those who did not state a monogamous relationship:	(n=330)	(n=287)
Would use condoms	240 73	199 69
Would have fewer partners/know partner well	179 54	94 33*

*Significant difference girls *v* boys (p<0·001).

before having intercourse and planned to have fewer partners.

Discussion

Farrell in her study in the mid 70s wrote about intercourse being part of a stable teenage relationship, although no specific definition of 'stable' was made.[2] Over three quarters of our population defined a steady relationship as going out with the same person for a certain number of weeks—the median being 10 weeks for girls and eight weeks for boys. For just under a half of the girls and between a third and a half of the boys this type of relationship was associated with intercourse and in the age range 15–17 years the existence of a serious relationship was a much stronger determinant of sexual activity than age. Most teenagers included within the framework of this definition a degree of exclusiveness and faithfulness.

The girls who started their periods early were more likely to be sexually active as has been previously reported in pregnant teenagers[1 3]; a possible explanation being that they are physically mature and engage in serious relationships at an earlier age but do not have the corresponding emotional maturity to realise the implications of sexual activity and possible pregnancy. The experienced girls were also subject to less supervision by their parents, thus providing them with more opportunities for intercourse as has been previously reported in the teenage pregnancy study.[1] Factors that differentiate virgin and experienced boys are not so clearly demonstrated.

Selection of schools in this study was made to give a cross section of school types and to ensure adequate representation of each social class group. The largest group of parents were from social class II and the majority were from the non-manual sector (I–IIIn) using the Registrar General's classification of father's occupation. This is explained by the rural area from which many pupils were drawn and by the fact that 25% of the study population were drawn from private schools. Significantly more girls who were experienced came from the lower social classes, but boys who were experienced came from all home backgrounds. There was no difference in terms of future plans and sexual activity except with the youngest girls.

The different rates of sexual activity between the comprehensive schools cannot be accounted for by a difference in social class distribution. The school itself appeared to have an effect on activity. It was difficult to assess whether this was related to the teenagers themselves, or to the environment and atmosphere of the school or to the curriculum, or a combination of these factors. The city school where the classrooms were locked between lessons, where there were few pictures on the wall, where children ate their lunch in the cloakroom, and where there appeared to be a large number of supply teachers, had a higher rate of sexual intercourse than either of the rural comprehensives that had a similar social class structure. Rates were not significantly different in the private schools, which had a much higher percentage of high social class families.

Most teenagers remembered teaching on the biological facts of reproduction, contraception, and sexually transmitted diseases and in a previously reported study there were requests for more non-biological teaching on relationships, pressures, etc. The efficacy of the teaching did appear to be related to the enthusiasm and commitment of the staff and the respect the teenagers had for the teachers.[4]

Sexual activity among teenagers is therefore not restricted to the non-academic from the lower socioeconomic groups but is regarded as a normal part of a relationship for teenagers of all abilities and background.

Previous studies noted a sex discrepancy in the number of teenagers who were sexually experienced in their mid teens.[2 5] Farrell, writing in the 1970s, suggested that 55% of males and 46% of females between 16 and 19 years had experienced intercourse. Examination of Farrell's data shows that 12% of all girls and 31% of all the boys said they first had intercourse before 16 years. In this study the numbers were very similar, and although the difference was not significant more girls were sexually active than boys at 15 years. This perhaps is what one would expect considering that girls mature physically earlier than boys and tend to go out with boys older than themselves. The number who are sexually active at 16 and 17 years is probably an underestimate because the sample did not include 16 and 17 year olds who had left school and might be expected to be more sexually active.

Experienced girls and boys were significantly more likely to have friends who were also perceived as being sexually active. Peer influence is a powerful pressure to conform to what is regarded as 'normal' behaviour.[6] The perception by girls that the boys are more active than they actually are was clearly seen in the overestimation of sexual activity of male friends. Although 40% of the teenagers involved in a steady or more serious relationship were sexually experienced only a quarter of the total teenage population studied were experienced. Most teenagers under 18 years are therefore not experienced and one ploy in education could be to attempt some reduction of this peer pressure and to encourage the normality of relationships without intercourse.

The effect of media on behaviour is difficult to quantify. Bury has stated that 'In relation to sexual matters there seems little doubt that television, films, pop culture and advertising have all affected behaviour by emphasising the glamour of sex . . . for some years now, and long before it was the case, the media has given the impression that most teenagers are sexually experienced'.[3]

If teenagers are sexually active in their mid teens it is common for them to have a series of exclusive sexual relationships before marriage,[4] which has been called serial monogamy.[3 7] Serial monogamy exposes each partner to their partners previous partners with the associated medical risks of sexually transmitted diseases and cervical cancer. Sexually transmitted diseases lead to the secondary problems of infertility and the risk of ectopic pregnancy in the girls; HIV infection leads to the major problem of acquired immune deficiency syndrome in both men and women.

The teenagers had a good understanding of how AIDS is transmitted and were reasonably knowledgeable as to what AIDS is. For most it was not seen as a problem that would personally affect them.

Although they knew AIDS was transmitted by sharing needles in drug abuse very few mentioned this aspect in describing what AIDS was and similarly few mentioned not being involved in the drug scene. This can probably be explained by that fact that for the majority drug abuse was not personally relevant to them.

Only a fifth of the teenagers anticipated having a single monogamous relationship. Of those who did not plan monogamy about three quarters mentioned using condoms. Contraceptive usage among young people is, however, haphazard,[8] often because intercourse is unplanned,[9] and the sheath has never been regarded as a reliable form of contraceptive in this age group.[10]

Significantly more of the girls than boys stated the importance of knowing their partner well before having intercourse and of planning to limit the number of partners they had. Previous studies have shown that boys tend to be more casual in sexual relationships,[4 9] and despite the AIDS campaign this attitude has not apparently altered.[5]

If education is to be effective in reducing the AIDS epidemic it must be sufficiently relevant to create and maintain changes in behaviour. As well as focusing on those groups particularly at risk it is also important to aim education programmes at young people before they have established patterns of behaviour.

Education is the responsibility of parents, school, and society as a whole. Previous evidence suggests that where parents exercise supervision and discuss such topics openly with their children, the children are less likely to become involved in early sexual activity,[11] and this study supports this especially in relation to girls. Health education programmes at school are aimed at helping children take responsibility for their own long term health. In the area of sex education it would be appropriate for there to be clear statements that early intercourse and multiple partners are associated with important medical risks including sexually transmitted diseases and HIV infection.

The present generation of teenagers is potentially most at risk of AIDS. There is an opportunity through education in its widest sense to reduce this risk before patterns of behaviour are established.

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References

[1] Curtis HA, Lawrence CJ, Tripp JH. Sexual intercourse and pregnancy. *Arch Dis Child* 1988;**63**:373–9.

[2] Farrell C. *'My mother said . . .'* London: Routledge and Keegan Paul, 1978.

[3] Bury J. *Teenage pregnancy in Britain.* London: Birth Control Trust, 1984.

[4] Curtis HA, Tripp JH, Lawrence C, Clarke WL. The influence of teenage relationships and sex education. *Arch Dis Child* 1988; **63**:935–41.

[5] Schofield M. *Sexual behaviour of young people.* London: Pelican, 1968.

[6] Osofsky JD, Osofsky HJ. Teenage pregnancy: psychosexual considerations. *Clin Obstet Gynaecol* 1978;**21**:1161–73.

[7] Sorensen RC. *Adolescent sexuality in contemporary America.* New York: World Publications, 1973.

[8] Ryde-Blanquist E. Contraception in adolescents: a review of the literature. *J Biosoc Sci* 1978;**suppl 5**:129–58.

[9] Zelnick M, Shah F. First intercourse among young americans. *Fam Plann Perspect* 1983;**2**:65–70.

[10] Fox LS. Adolescent male reproductive responsibility. *Social Work in Education* 1983;**6**:32–43.

[11] Inazu J, Fox GL. Maternal influences on the sexual behaviour of teenage daughters. *Journal of Family Issues* 1980;**11**:81–102.

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Bronchoalveolar lavage in HIV infected patients with interstitial pneumonitis

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SUMMARY The value of taking microbiological and cytological specimens by flexible bronchoscopy and bronchoalveolar lavage under local anaesthesia was assessed on 43 occasions in 35 HIV infected children, aged 3 months to 16 years, with interstitial pneumonitis. In acute interstitial pneumonitis (n=22, 26 specimens from bronchoalveolar lavages) the microbiological yield was 73%, *Pneumocystis carinii* being the commonest infective agent (n=14). *P carinii* pneumonia was found only in children with deficient antigen induced lymphocyte proliferative responses who had not been treated with long term prophylactic co-trimoxazole. In contrast, in 13 children with chronic interstitial pneumonitis that was consistent with a diagnosis of pulmonary lymphoid hyperplasia who underwent bronchoalveolar lavage on 17 occasions, there were two isolates of cytomegalovirus and one of adenovirus, but *P carinii* was not found. Ten of the 13 children had normal antigen induced lymphocyte proliferative responses. Useful cytological data were also gleaned from bronchoalveolar lavage specimens. Lymphocytosis was significantly higher in pulmonary lymphoid hyperplasia (36(SD 11)%) than in *P carinii* pneumonia (24(19)%) whereas the percentage of polymorphonuclear neutrophils was significantly lower (3(2)% compared with 12(13)%). Flexible bronchoscopy with bronchoalveolar lavage is safe even in young infants and should reduce the necessity for open lung biopsy in the management of HIV infected children with interstitial pneumonitis.

Pulmonary complications, particularly interstitial pneumonitis, are common among HIV infected children. *Pneumocystis carinii* infection usually causes acute interstitial pneumonitis and pulmonary lymphoid hyperplasia causes chronic interstitial pneumonitis.[1 2] In adults fibreoptic bronchoscopy and bronchoalveolar lavage are useful in the investigation of interstitial pneumonitis.[3 4] Experience in children is still limited[5–8] and open lung biopsy was until recently the main method of diagnosis.[1 9 10] Our experience of flexible bronchoscopy in young children[11] and of bronchoalveolar lavage in immunocompromised children[12] led us to assess the diagnostic value of microbiological and cytological examination of bronchoalveolar lavage specimens in HIV infected children with interstitial pneumonitis.

Patients and methods

Thirty five children (24 boys and 11 girls) aged between 3 months and 16 years (mean age 3 years 2 months) underwent bronchoalveolar lavage 43 times between June 1983 and December 1987. Fourteen of these children were less than 1 year old and only five were over 7 years old. The diagnosis was made from a positive serological HIV response by western blot (Pasteur Diagnostics). For those children less than 15 months old whose mothers had positive serological responses, a virus culture or detection of the P25 antigen in the serum with a monoclonal antibody (Abbott Laboratories), or both, was required to eliminate the possibility of passively transmitted maternal antibody. HIV was transmitted from infected mothers to their offspring in 27 cases and by blood products in eight. All these children were in subgroup P2 of the Centers for Disease Control classification for HIV infections in children.[13] The immunological study included an analysis of the number of cluster determinant 4 (CD4) lymphocytes in the peripheral circulation by immunofluorescence (Ortho), and measurement of lymphocyte proliferative capacity after stimulation by at least two different antigens.[14] Independently of their clinical state and history of infection two groups of children were identified by their proliferative response in the presence of antigen. This was positive in group 1 (n=15) and negative in group 2 (n=20), indicating a severe deficiency in cellular immunity as recently shown by Blanche *et al.*[15]

PULMONARY DISORDERS

Acute interstitial pneumonitis

Twenty six bronchoalveolar lavage specimens were taken from 22 children with acute interstitial pneumonitis diagnosed on physical findings and chest radiography. The mean (SD) interval between the onset of interstitial pneumonitis and bronchoalveolar lavage was 11 (6) days. Five of the children were from group 1 and 17 from group 2. In eight cases the pneumonitis was only moderate, but in 14 it was severe with hypoxaemia that required treatment with nasal oxygen. Four children had second bronchoalveolar lavage specimens taken two weeks after treatment had been started because of relapse of dyspnoea and fever. At the time of the first bronchoalveolar lavage 18 children were not treated or were treated for less than a week with cotrimoxazole.

Chronic interstitial pneumonitis

Seventeen bronchoalveolar lavage specimens were taken from 13 children with chronic interstitial pneumonitis that had been present for a mean (SD) 9 (6) months and the procedure was carried out when they were stable clinically. Ten children were from group 1 and three from group 2. They all had stable radiographs showing diffuse nodular or reticulonodular lung patterns. This type of interstitial pneumonitis was associated with cervical lymphadenopathy (all cases), parotitis (9/13), hepatosplenomegaly (9/13), clubbing of the fingers (5/13), and shortness of breath on exertion (7/13). Hypergammaglobulinaemia (>30 g/l) was present in all cases. This picture was consistent with the diagnosis of pulmonary lymphoid hyperplasia.[1]

PROCEDURES

Flexible bronchoscopy, bronchoalveolar lavage, and lavage fluid analysis were carried out as previously described.[12] All except one of the bronchoscopies were carried out under local anaesthesia after premedication that usually comprised atropine (0·01 mg/kg given subcutaneously) one hour before the procedure and midazolam (0·3–0·5 mg/kg) or diazepam (0·5 mg/kg) given rectally 10–15 minutes before examination. Two fibreoptic bronchoscopes were used, the Olympus BF 3C10 for children aged less than 7 years and the Olympus BF 4B2 for older children. In the youngest children, and whenever interstitial pneumonitis was severe, the procedures were carried out while the patients were receiving oxygen through the other nostril. Once the tracheobronchial tree had been examined, the bronchoscope was wedged in a lobar or segmental bronchus, usually the middle lobe or the right lower lobe. An initial sample (5–10 ml) of prewarmed physiological saline was injected and then aspirated. This initial sample was discarded as being of bronchial origin. Several samples were then injected and aspirated up to a maximum volume of 10% of the functional residual capacity. The recovered liquid was used for microbiological and cytological studies: part of it was used for immunofluorescence screening (for *Legionella pneumophila*, respiratory syncytial virus, parainfluenza virus, herpes simplex virus, cytomegalovirus, and adenovirus), and cultures for viruses, bacteria, fungi, and mycobacteria. A total cell count of nucleated cells was done on the lavage fluid, and 12 Cytospin preparations were made by cytocentrifugation at 30 *g* for 10 minutes on a Cytospin 2 (Shandon Southern Instruments). These were stained by May Grünwald Giemsa, periodic acid Schiff (PAS), Gram, Grocott, Ziehl, and Perls, and examined for cytological evidence of fungal, viral, and parasitic infection and for the presence of siderocytes. The remaining fluid was cytocentrifuged for 10 minutes at 60 *g*, the sediment was fixed in Bouin's solution and embedded in paraffin, and histological sections were cut and stained with haematoxylin and eosin, PAS, and Grocott.

Data were analysed by Student's *t* test and the χ^2 test. A p value of less than 0·05 was accepted as significant.

Results

TOLERANCE

No complications were encountered during or after flexible bronchoscopy and bronchoalveolar lavage. The mean fluid return was 65%. No case of respiratory decompensation or of transfer to the intensive care unit could be attributed to the procedure. Treatment with oxygen by nasal tube prevented drops in arterial oxygen pressure in even the most hypoxic and youngest children. A transient spike of fever occurred in 13 (30%) of the children four to six hours after the bronchoalveolar lavage.

MICROBIOLOGICAL RESULTS

Acute interstitial pneumonitis

Bronchoalveolar lavage specimens gave diagnostic

Table 1 *Organisms isolated from the bronchoalveolar lavage fluid in 26 patients with acute interstitial pneumonitis*

Organism	*No of patients*
P carinii	17
L pneumophila	1
Cytomegalovirus	3
Respiratory syncytial virus	1
Parainfluenza 3 virus	1
Mixed infections	3

information in 19 of the 26 examinations (73%) (table 1). The most common organism isolated was *P carinii* (n=17), which was found in 14 of 17 children in group 2 and in none of the five children in group 1 (p<0·001). *P carinii* was still present in three of the four treated children who were re-examined on the 15th day, and in 14 of the 18 children who were not treated or treated for less than a week with co-trimoxazole. It was not found in the four children treated for over a month. Three mixed infections were observed: *P carinii* and cytomegalovirus in two cases, and *P carinii*, *L pneumophila* and parainfluenza 3 virus in the other.

Chronic interstitial pneumonitis

Only two isolates of cytomegalovirus and one of adenovirus were found in 17 bronchoalveolar lavage specimens; no *P carinii* was identified.

When both acute and chronic interstitial pneumonitis were considered together, *P carinii* was found in none of the 15 children in group 1 and in 14 of the 20 in group 2 (p<0·001).

CYTOLOGICAL RESULTS

The data are summarised in table 2. In both acute and chronic interstitial pneumonitis there was an increase in the total cell count with a significant increase in lymphocytes, and a moderate increase in neutrophils.[14] Lymphocytosis (SD) (36(11)%) was significantly higher in the patients with pulmonary lymphoid hyperplasia than in acute interstitial pneumonitis (17(19)%, p<0·0005), in acute interstitial pneumonitis with *P carinii* (24(19)%, p<0·05), and in acute interstitial pneumonitis without *P carinii* (13(19%), p<0·0005). The mean percentage of neutrophils (12(13)%) was significantly higher in acute interstitial pneumonitis with *P carinii* than in acute interstitial pneumonitis without *P carinii* (2(3)%, p<0·05) and in pulmonary lymphoid hyperplasia (3(2)%, p<0·005).

OUTCOME OF ACUTE INTERSTITIAL PNEUMONITIS

Co-trimoxazole treatment was effective in 12 of the 14 children with *P carinii* pneumonitis, and two children died.

Discussion

These results confirm that flexible bronchoscopy and bronchoalveolar lavage carried out by an experienced paediatric bronchoscopist can be performed safely even in young infants and is well tolerated and useful in children infected with HIV with acute and chronic interstitial pneumonitis.[5 12 17]

During acute interstitial pneumonitis, the overall microbiological yield of bronchoalveolar lavage was 75%, and *P carinii* was the predominant opportunistic infective agent (63%), which is similar to results obtained in AIDS related interstitial pneumonitis in adults[3 18 19] as well as in children.[5 20] In the series of Bye *et al*,[5] microbiological analysis of 14 aspirates from bronchoalveolar lavage from 29 children with AIDS and AIDS related complex and acute respiratory illness grew *P carinii*. The diagnostic yield of *P carinii* pneumonia can be improved in adults by doing transbronchial biopsies.[4] Transbronchial biopsy, however, cannot be carried out safely in children younger than 7 years old.[21] Only five children in the present series could have benefited from such exploration, but all had *P carinii* in the bronchoalveolar lavage. None of the children taking part in this study had open lung biopsy, and all those who had had a negative bronchoalveolar lavage (25%) recovered completely. The episodes of interstitial pneumonitis in which no infective agent was identified may have several explanations: bronchoalveolar lavage may have been carried out in a

Table 2 *Results of cytology of 43 samples of bronchoalveolar lavage fluid from 35 children with HIV infection; 26 had acute interstitial pneumonitis and 17 chronic pulmonary lymphoid hyperplasia. Results are expressed as mean (SEM)*

	Cells *(10^3/ml)*	% *Macrophages*	% *Lymphocytes*	% *Neutrophils*
Pulmonary lymphoid hyperplasia (n=17)	413 (48)	62 (2·7)	36 (2·7) *	** 3 (2·9)
Interstitial pneumonitis with *P carinii* (n=17)	383 (49)	63 (5·8)	** 24 (4·6)	12 (3·2) *
Interstitial pneumonitis without *P carinii* (n=9)	474 (119)	84 (3·0)	13 (3·0)	2 (1·0)

*p<0·05; **p<0·005.

child who had been on co-trimoxazole for at least a month, there may have been undocumented viral infection, or interstitial pneumonitis may have been due to the HIV itself. The sensitivity and specificity of bronchoalveolar lavage compared with open lung biopsy cannot be evaluated in our HIV infected children, but our results confirm those of Suffredini *et al*[18] and those of Bye *et al.*[5] In the study of Suffredini *et al,* 32% of 152 episodes of interstitial pneumonitis diagnosed by bronchoalveolar lavage and transbronchial biopsy had non-specific lesions without a detectable infective agent. In the study of Bye *et al* 12 of 29 children with acute respiratory illnesses had sterile bronchoalveolar lavage fluid: open lung biopsy (n=4) or necropsy (n=3) did not show any false negative lavages. The association between the patient's immunological state and the presence of *P carinii* should be emphasised. *P carinii* pneumonia was observed only in children in group 2 (with deficient cellular immunity) who were either insufficiently treated or not treated. In eight of 14 children *P carinii* pneumonia was the symptom leading to the diagnosis of HIV infection. All these immunological and retrospective data suggest that prophylactic treatment with co-trimoxazole is justified and it is noteworthy that during the same period none of 34 children admitted for HIV infection and given prophylactic co-trimoxazole because of their altered immune state, developed *P carinii* pneumonia (S Blanche, unpublished observations).

Bronchoalveolar lavage also provides useful cytological information. The increase in total cell counts and lymphocytes and the moderate increase in polymorphonuclear neutrophils, are well known in adults,[22-25] but have not previously been reported in children. Cytologically, *P carinii* pneumonia produces clumps of cellular debris, lymphocytosis (24(19)%) and an increase in polymorphonuclear neutrophils (12(13)%). These anomalies were significantly different from those seen in acute interstitial pneumonitis in which *P carinii* has not been identified. In contrast with the results of Smith *et al,*[26] the increase in polymorphonuclear neutrophils was not associated with a more severe clinical or radiological course.

Pulmonary lymphoid hyperplasia represents a special entity. Although this diagnosis has been, until now, histological,[13] the clinical, radiological, and laboratory picture and the slow progressive course are now so characteristic that open lung biopsy is no longer routinely required.[1 20 27] In pulmonary lymphoid hyperplasia, bronchoalveolar lavage provides supplementary diagnostic evidence, both confirming the absence of opportunistic infection[1 27] and showing a large increase in lymphocytes without a corresponding increase in polymorphonuclear neutrophils.[24-27] Mean percentages of lymphocytes and neutrophils were significantly different from those found in children with *P carinii* pneumonia. In none of the 17 bronchoalveolar lavages was *P carinii* identified; only two grew cytomegalovirus, and one an adenovirus. This absence of *P carinii* infection should be correlated with the immune state of this group of children: 10 of 13 were in group 1 and had normal antigen induced lymphocyte proliferation. Here again, although the Centers for Disease Control criteria include *P carinii* pneumonia and pulmonary lymphoid hyperplasia in the same P2 subgroup, the two diseases are quite different in several points (especially immunological), and the better medium term prognosis for cases of pulmonary lymphoid hyperplasia.[1 15] The mechanism of this lymphocytosis is not yet known. There is a latent lymphocytic alveolitis that is probably specific and linked to the HIV virus itself.[28 29] The development of pulmonary lymphoid hyperplasia might be the result of an increase in this alveolitis and occur under the influence of a cofactor, such as Epstein-Barr virus.[29]

In conclusion, flexible bronchoscopy and bronchoalveolar lavage should be advocated as a primary procedure in the exploration of interstitial pneumonitis in children infected with HIV. The detection of opportunistic infections especially *P carinii* should decrease the indications for open lung biopsy, which should be reserved for children in whom bronchoscopy was not diagnostic and whose clinical condition was deteriorating. Similarly, the presence of lymphocytosis alone in the absence of *P carinii* and the absence of an increased proportion of neutrophils should also provide additional evidence in children with clinical and radiological suspicion of pulmonary lymphoid hyperplasia.

References

1 Barbour SE. Acquired immunodeficiency syndrome in childhood. *Pediatr Clin North Am* 1987;**34**:247–68.

2 Rubinstein A, Morecki R, Silverman B, *et al.* Pulmonary disease in children with acquired immune deficiency syndrome and AIDS-related complex. *J Pediatr* 1986;**108**:498–503.

3 Orenstein M, Webber CA, Cash M, *et al.* Value of bronchoalveolar lavage in the diagnosis of pulmonary infection in acquired immune deficiency syndrome. *Thorax* 1986;**41**:345–9.

4 Murray JF, Garay SM, Hopewell PC, *et al.* Pulmonary complications of the acquired immunodeficiency syndrome: an update. *Am Rev Respir Dis* 1987;**135**:504–9.

5 Bye MR, Bernstein L, Shah K, *et al.* Diagnostic bronchoalveolar lavage in children with AIDS. *Pediatr Pulmonol* 1987;**3**:425–8.

6 de Blic J, McKelvie P, Le Bourgeois M, *et al.* Bronchoalveolar lavage in children with acquired immunodeficiency syndrome. *Am Rev Respir Dis* 1987;**135**:A72.

7 Frankel LR, Smith DW, Lewiston NJ. Bronchoalveolar lavage for diagnosis of pneumonia in the immunocompromised child. *Pediatrics* 1988;**81**:785–8.

8 Pattisthall EN, Noyes BE, Orenstein DM. Use of broncho-

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Cows' milk sensitive enteropathy in cystic fibrosis

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SUMMARY Proximal small intestinal mucosal biopsies were carried out in children with cystic fibrosis who had diarrhoea and failed to thrive in spite of adequate treatment, including pancreatic supplements. Histological examination of eight of the 17 biopsies taken over a period of 12 years showed evidence of enteropathy, and accounted for one in 13 (8%) children with cystic fibrosis under 3 years of age attending our clinic. Seven responded to a cows' milk free diet; the diarrhoea stopped and weight gain increased. One of these responded only when gluten was also excluded from his diet. The eighth child remained on a normal diet and his symptoms did not improve. The enteropathy had resolved in all five patients who had further biopsies taken while receiving treatment, and from 15 months to 3 years of age all the children tolerated a normal diet and continued to thrive.

Cows' milk sensitive enteropathy is an important cause of failure to thrive in children with cystic fibrosis. Small intestinal biopsy is an important investigation in younger children who fail to thrive and have diarrhoea despite adequate treatment.

Children with cystic fibrosis often fail to thrive. This failure is usually related to the disease itself, and may be the result of recurrent chest infections, inadequate food, or pancreatic enzyme deficiency. Two gastrointestinal diseases that may, in association with cystic fibrosis, cause failure to thrive are coeliac disease[1 2] and lactase deficiency.[3 4]

It is important to make the correct diagnosis when a child with cystic fibrosis is failing to thrive as the severity of the respiratory component of the disease (which may affect prognosis) seems to be related to the child's nutritional state.[5] The aim of this study was to investigate whether cows' milk sensitive enteropathy is a cause of chronic diarrhoea and failure to thrive in children with cystic fibrosis.

Patients and methods

Seventeen children were included in the study from 1975–1987. Fifteen of the patients were already attending the cystic fibrosis clinic and were selected for small intestinal mucosal biopsy because they were failing to thrive in spite of adequate treatment for cystic fibrosis. This included pancreatic enzyme and fat soluble vitamin supplements. Two other children underwent small intestinal mucosal biopsy and sweat tests during the same admission as part of the routine procedure for investigation of failure to thrive, and had positive sweat tests. They were taking no medication at the time of biopsy. The weights of all the children were below the 25th percentile, and five were well below the third.

Nine of the children were boys and eight girls. They were aged from 3 months to 12 years (median 12 months). In all cases the diagnosis of cystic fibrosis was made from two positive sweat tests and typical symptoms. Sweat tests were considered positive if at least 100 mg of sweat was collected that contained at least 70 mmol/l sodium.

The diagnosis of cows' milk sensitive enteropathy was made when characteristic histological findings were present in a proximal small intestinal mucosal biopsy specimen,[6] and there was a rapid clinical response to the exclusion of cows' milk from the diet.[7] Early challenge with cows' milk and further small intestinal biopsies were necessary to prove that the disease was present. In practice, as the condition was a temporary one and there was a risk of anaphylaxis on the reintroduction of cows' milk, challenge was not considered necessary if the histology was characteristic and the clinical improvement rapid.

At the time of small intestinal mucosal biopsy, 16 of the children were on cows' milk based feeds, and one was breast fed. The mother of the latter child included cows' milk in her diet. Three children under 6 months old were on full fat adapted formula feeds, three were taking 'cystic mix' (SMA and

Marvel with added Caloreen), and the other 10 were having skimmed milk. The 13 oldest children included a normal amount of gluten in their diets, but the four youngest had not started solids. Stool samples were taken from all patients and examined for pathogens. The small intestinal mucosal biospy specimens were taken after full informed consent had been given by the parents.

After an overnight fast, a paediatric sized double port capsule was used to obtain mucosa from the duodenojejunal flexure under radiological control. In addition to the biopsy specimen, duodenal juice was aspirated if possible and examined for the presence of *Giardia lamblia.* A sample of tissue from one biopsy specimen from each patient was frozen in liquid nitrogen and used to assay disaccharidases,[8] and the other was fixed in formal saline and processed for histological examination. Suitable specimens were also analysed morphometrically using a computer based image analysis system.[6] If the histological appearance of a biopsy was abnormal and consistent with a cows' milk sensitive enteropathy[6] the child was given a cows' milk exclusion diet for the next few months, usually until at least 15 to 18 months of age. These children were reviewed regularly in the outpatient clinic with particular attention being paid to weight gain and stool frequency. If possible proximal small intestinal mucosal biopsy was repeated before cows' milk was reintroduced to their diets. Morphometric analysis of the biopsy specimens was again performed and the results were compared with those of the specimens obtained on presentation.

Other features of the children with enteropathies that were reviewed were: the manner of initial presentation with cystic fibrosis; a personal or family history of atopy; and any investigations which might have indicated an atopic tendency. These included examination of peripheral blood for eosinophils, skin prick tests for allergens, and estimation of serum IgE and specific IgE concentrations. Sixteen per cent of all children attending our clinic during the 12 year period presented with meconium ileus.

Results

In nine of the 17 children proximal small intestinal biopsy specimens were histologically normal. They were aged from 3 months to 12 years (median 2 years). Seven were girls and two boys. No pathogenic organisms were detected in their stool samples, and *G lamblia* was not detected in any duodenal aspirate. No gastrointestinal cause other than cystic fibrosis was found to explain their failure to thrive and chronic diarrhoea.

Histological and morphometric findings in the biopsy specimens from the remaining eight children were abnormal and consistent with cows' milk sensitive enteropathy—that is, they had thin mucosa with reduced villous height (fig 1). Seven of these children were boys, and their ages ranged from 5 months to 28 months (median 10). This group included one of the children who underwent small intestinal mucosal biopsy at the same time as cystic fibrosis was diagnosed. Rotavirus was detected by electron microscopy both in the stool and within the small intestinal mucosa of one child. No pathogens were detected in stool or duodenal aspirate from any other patient.

The child with most frequent diarrhoea (10 times a day) had an enteropathy, while the child without diarrhoea did not. Apart from these two cases, there was no obvious difference in stool output between those children with enteropathy and those with normal small intestinal mucosa.

Patients with enteropathy were on a variety of cows' milk based feeds. Three were on formula feeds, two were on cystic mix, one was on doorstep milk, and the other two on skimmed milk.

Four of the eight children with enteropathy had originally presented with meconium ileus, whereas about 16% of all children attending the clinic over the 12 years had presented in this manner. The other four had presented with failure to thrive, and one also had recurrent chest infections. At the time of small intestinal mucosal biopsy the weights of five were below the third percentile (and the other three on or below the 10th), all their birth weights had

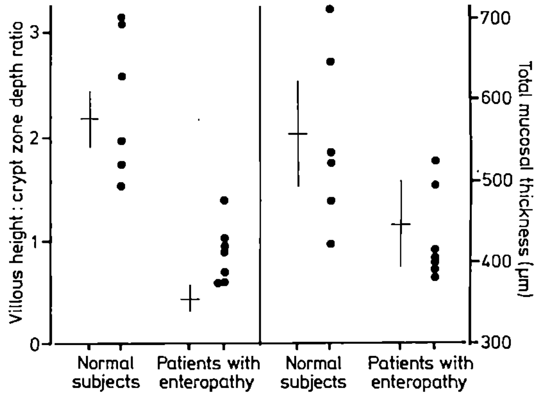

Fig 1 *Morphometric findings in patients with and without cows' milk sensitive enteropathy. Dots represent the 13 patients studied, and vertical bars the findings of Maluenda et al (mean (SD)).*[6]

been in the normal range. All seven available for follow up had developed atopic symptoms, which included asthma in five, eczema in two, and urticaria in one. Three children had appreciable eosinophilia (more than 400×10^6/l) on at least one occasion.

Disaccharidase activities were normal in the four histologically normal biopsy specimens in which they were measured. Sucrase and maltase activities were normal in the six children with enteropathy in which they were measured. Lactase activity was reduced in two (0·5 and 0·8 mmol/min/g). This was not associated with clinical lactose intolerance in either child.

Seven of the eight children with small bowel mucosal abnormalities compatible with the diagnosis of cows' milk sensitive enteropathy had cows' milk withdrawn from their diets; Pregestimil was used as a substitute feed. The diagnosis does not seem to have been considered in one child who was biopsied in 1976, who remained on cows' milk, and who continued to fail to thrive. He died from a chest infection aged 3 years.

In six of the seven children stool consistency improved, stool frequency fell to two or three times a day, and they had 'catch up' weight gain. One child whose weight on presentation was well below the third percentile (3·6 kg at 6 months) almost reached this percentile in six months. One child's weight climbed from the third to the 10th percentile, two from the tenth to the 25th, and two reached the 50th percentile (one from the third and the other from the 10th).

The one child who did not improve rapidly underwent a further proximal small intestinal biopsy, which showed that enteropathy was still present. Gluten was excluded from his diet in addition to cows' milk, and a third biopsy showed improvement in the histological picture. He underwent two further biopsies, both of which were normal. The first was at 3 years of age after cows' milk was reintroduced to his diet, and the other at 4 years of age when his diet also included gluten, so he had transient gluten intolerance rather than coelic disease.

Small intestinal biopsy was also repeated in four of the seven other children with enteropathy 2–14 months later while they were receiving cows' milk free diets. Reasons for not repeating the biopsy in the other three were: adverse social circumstances (n=1), follow up continued elsewhere (n=1), and cows' milk sensitive enteropathy not recognised (n=1). All five biopsy specimens showed obvious improvement on histological examination.

Four of the five specimens were suitable for morphometric analysis. Fig 2 shows the results of morphometry in these, and compares them with the morphometric findings on presentation. In four the mucosal thickness improved, and in all cases the ratio of villous height:crypt zone depth improved.

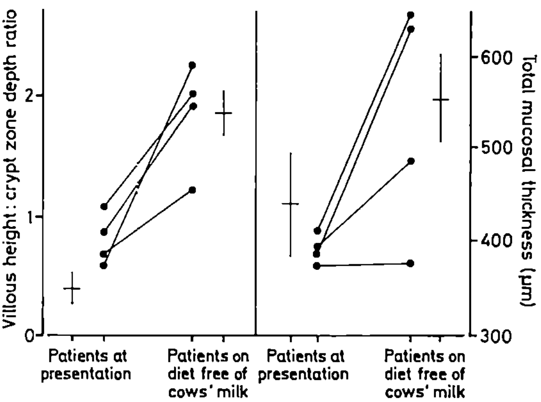

Fig 2 *Morphometric findings in patients with cows' milk sensitive enteropathy on presentation and on a diet free of cows' milk. Dots represent the four patients biopsied twice, and vertical bars the findings of Maluenda et al (mean (SD)).*[6]

Disaccharidase activities were again measured, and the child who had had the lowest lactase activity now had one within the normal range (1·8).

The children were challenged with cows' milk from 2–13 months (median 10 months) after excluding it from their diets. There were no adverse reactions, weight gain continued at the same rate as previously, and stool frequency was unchanged.

Discussion

Cows' milk sensitive enteropathy was a common problem among the children under 3 years old (8/13, 62%) who were selected from our cystic fibrosis clinic for small intestinal mucosal biopsy. As 105 children had presented to our clinic by 3 years of age from 1975–87, the overall incidence of the enteropathy in children presenting with cystic fibrosis in this age group was 1/13. The incidence of cows' milk sensitive enteropathy in the general population is difficult to establish, particularly as so many children are started on restricted diets without seeing a doctor, but it seems to be considerably lower than this.[9]

Three possible reasons for a high incidence in children with cystic fibrosis are: the association of cystic fibrosis with atopy[10] (cows' milk sensitive enteropathy is an atopic related disorder), increased intestinal permeability,[11] and impaired digestion of protein due to insufficient pancreatic trypsin leading to a high antigen load presenting to the small intestinal mucosa.

The main features of this group of patients were the unequal sex ratio, the high incidence of atopy, and the presentation with meconium ileus. A predominence of boys with a family history of atopy has previously been reported in a group of children presenting with cows' milk sensitivity.[12] Atopic symptoms are common in children with cows' milk sensitive enteropathy alone,[13] and as already mentioned atopy is associated with cystic fibrosis.[10] The incidence of meconium ileus would of course be higher in this group than among all children with cystic fibrosis, as cows' milk sensitive enteropathy is a disease of infancy, and many children with cystic fibrosis present later. The incidence of 50% is surprisingly high, however, when the overall incidence in our clinic was 16%.

In some cases, although the mucosal appearance had improved when cows' milk was excluded from the diet, it was not entirely normal. This is similar to previous findings[6] and could indicate that in spite of advice from a dietitian these children may have continued to ingest some cows' milk. Alternatively they may have reacted to Pregestimil or other dietary constituents, although this was not clinically apparent. One child was intolerant of gluten, which illustrates the fact that multiple food intolerances may co-exist.[14] It was because of this that Pregestimil was used as a cows' milk substitute (rather than a soya based milk), because at least 15% of children intolerant of cows' milk also react to soya milk.[7] As all the children treated for cows' milk sensitive enteropathy were given Pregestimil feeds, there were no 'control' children. It could be argued that children with cystic fibrosis, even without cows' milk sensitive enteropathy, would thrive better on Pregestimil than cows' milk feeds because Pregestimil contains fat in the form of medium chain triglycerides which are water miscible and more rapidly hydrolysed by pancreatic lipase than long chain triglycerides. Cows' milk feeds, however, do have the advantages of higher salt and protein contents. When our group of children were restarted on diets containing cows' milk there were no noticeable changes in the rate of weight gain, so there was no evidence that either milk was superior once tolerance to cows' milk had been achieved.

Although cases of cows' milk sensitive enteropathy in patients with cystic fibrosis do not seem to have been reported previously, the enteropathy may have been described.[4 15 16] Antonowicz *et al* reported 27 cases of cystic fibrosis with steatorrhoea in association with small bowel enteropathy; no explanation for the enteropathies was given.[4] Reduction in disaccharidase activities was thought to be secondary to the partial villous atrophy (as in our two cases with low activities of lactase on presentation). Nordio *et al* also described a child with reduced disaccharidases 'associated with a flatness of intestinal mucosa'.[15] Of 17 children with cystic fibrosis described by Gibbons, the one patient with clinical and biochemical evidence of lactase intolerance underwent small intestinal biopsy.[16] There was flattening of the mucosa with villous atrophy and reduced disaccharidase activity. No explanation was given for the enteropathy. In view of our findings, it seems likely that some of these cases were of cows' milk sensitive enteropathy.

Only two of our children had low lactase activity on presentation, and there was no evidence of lactose intolerance. Lactase deficiency has been associated with cystic fibrosis in the past.[3 4 15 16] There was a single case report of lactase deficiency in a 3 year old boy in 1963,[3] and three cases were reported in 1966.[15] In 1968 seven cases were described[4] and a genetic association with cystic fibrosis was postulated, but on review 10 years later[17] the incidence was considered to be no higher than in the general population and was thus thought not to be secondary to cystic fibrosis. Other reports have been inadequate as either the diagnosis of cystic fibrosis was in doubt as sweat tests were normal,[18] or a lactose load did not cause diarrhoea.[16]

In conclusion, cows' milk sensitive enteropathy should be considered in the differential diagnosis of persistent failure to thrive in younger children with cystic fibrosis, particularly in view of our high incidence of 1/13 in patients under 3 years of age. We would not recommend a cows' milk free diet for newly diagnosed infants with cystic fibrosis if they are gaining weight well and have formed stools on treatment with pancreatic supplements, but there may be a place for giving a medium chain triglyceride containing protein hydrolysate formula feed plus pancreatic supplements to newly diagnosed infants who have frequent stools and poor weight gain on treatment with a suitable cows' milk based feed and pancreatic supplements. Some clinicians, however, might prefer to do a small intestinal biopsy first to exclude the rare case of coeliac disease. It is important to make the diagnosis and treat correctly as optimal nutritional state is thought to have such a profound effect on overall health, and possibly survival.[19 20] Recurrent respiratory infections, which can result in reduced life expectancy, are thought to be less of a problem in a child in a good nutritional state,[5] and this study shows that cows' milk elimination has an appreciable impact on the nutritional state of some patients with cystic fibrosis.

References

[1] Anderson DH. Cystic fibrosis of the pancreas and its relation to

coeliac disease. A clinical pathology study. *Am J Dis Child* 1938;**56**:344–99.

[2] Taylor B, Sokol G. Cystic fibrosis and coeliac disease: report of two cases. *Arch Dis Child* 1973;**48**:692–6.

[3] Cozetto FJ. Intestinal lactase deficiency in a patient with cystic fibrosis: report of a case with enzyme assay. *Pediatrics* 1963;**32**: 633–6.

[4] Antonowicz I, Reddy V, Khaw KT, Shwachman H. Lactase deficiency in patients with cystic fibrosis. *J Pediatr* 1968;**42**: 492–500.

[5] Sheppard R, Cooksley WGE, Cook WDD. Improved growth and clinical nutrition and respiratory changes in response to nutritional therapy in cystic fibrosis. *J Pediatr* 1980;**97**:351–7.

[6] Maluenda C, Phillips AD, Briddon A, Walker-Smith JA. Quantitative analysis of small intestinal mucosa in cows' milk sensitive enteropathy. *J Pediatr Gastroenterol Nutr* 1984;**3**: 349–56.

[7] Walker-Smith JA. Milk intolerance in children. *Clin Allergy* 1986;**16**:183–90.

[8] Phillips AD, Avigad S, Sacks J, Rice SJ, Walker-Smith JA. Microvillous surface area in secondary disaccharidase deficiency. *Gut* 1980;**21**:44–8.

[9] Rona RJ, Chinn S. Parents' perception of food intolerance in primary school children. *Br Med J* 1987;**294**:863–6.

[10] Hodson ME, Warner JO. Immunology. In: Hodson ME, Norman AP, Batten JC, eds. *Cystic fibrosis*. London: Ballière Tindall, 1983:91–6.

[11] Leclercq-Foucart J, Forget PP, Van Cutsem JL. Lactulose-rhamnose intestinal permeability in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1987;**6**:66–70.

[12] Halpem SR, Sellars WA, Johnson RB, Anderson DW, Sapenstein S, Reisch JS. Development of allergy in children fed breast, soy or cows' milk in the first six months of life. *J Allergy Clin Immunol* 1973;**51**:139–51.

[13] Digeon B, Walker-Smith JA. Food intolerance and gastrointestinal disease in infancy: personal practice. *Dig Dis* 1986;**4**: 139–46.

[14] Vitoria JC, Camarero C, Cojo A, Ruiz A, Rodrigukez-Soriano J. Enteropathy related to fish, rice and chicken. *Arch Dis Child* 1982;**57**:44–8.

[15] Nordio S, Lamedica GM, Beno A, Vignolo L. Disaccharidase activities of duodenal mucosa in children. *Ann Pediatr* 1966;**206**: 287–312.

[16] Gibbons ISE. Disaccharidases and cystic fibrosis of the pancreas. *Arch Dis Child* 1969;**44**:63–8.

[17] Antonowicz I, Lebenthal E, Shwachman H. Disaccharidase activities in small intestinal mucosa in patients with cystic fibrosis. *J Pediatr* 1978;**92**:214–9.

[18] Jones RHT. Disaccharide intolerance and mucoviscidosis. *Lancet* 1964;**ii**:120–1.

[19] Goodchild M. Practical management of nutrition and gastrointestinal tract in cystic fibrosis. *J R Soc Med* 1986;**79**(suppl 12): 32–5.

[20] Levy LD, Durie PR, Pencharz PB, Corey L. Effects of long-term nutritional rehabilitation on body composition and clinical status in malnourished children and adolescents with cystic fibrosis. *J Pediatr* 1985;**107**:225–30.

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Rectal mucosa in cows' milk allergy

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SUMMARY Eleven infants who were suspected clinically of having cows' milk protein sensitive enteropathy were fed with a protein hydrolysate formula for six to eight weeks, after which they had jejunal and rectal biopsies taken before and 24 hours after challenge with cows' milk protein. When challenged six infants (group 1) developed clinical symptoms and five did not (group 2). In group 1 the lesions developed in both the jejunal mucosa (four infants at 24 hours and one at three days), and the rectal mucosa, and the injury was associated with depletion of alkaline phosphatase activity. Infants in group 2 were normal. It seems that rectal injury that develops as a direct consequence of oral challenge with the protein in reactive infants may be used as one of the measurements to confirm the diagnosis of cows' milk protein sensitive enteropathy. Moreover, ingestion of such food proteins may injure the distal colonic mucosa without affecting the proximal small gut in some infants.

Injury to the mucosa of the proximal small bowel is a characteristic feature of food protein sensitive gastrointestinal allergy.[1-3] The pathogenesis and the appearance of clinical symptoms depends on several interdependent factors including the integrity of the immunodigestive barriers that modulate the movement of macromolecules across the gut,[4] the severity and extent of villous damage caused by the protein,[5] the types of immune responses triggered by the protein,[6-10] the presence of enteric infections[11] and others.[4 12] At present it is not known whether the whole gut is potentially sensitive to the offending food protein in a reactive infant. In a retrospective study of 53 patients aged 15 days to 17 years suspected of gastrointestinal allergy, Goldman and Proujansky noted that they could separate their series of cases into two groups with the principal effects in the rectum and colon on the one hand, and in the small bowel mucosa on the other.[13] In their study only 10 patients were biopsied at both sites, and it is not clear whether these infants had food protein intolerance because in some the exclusion diet brought no relief. We have previously noted development of mucosal lesions in both the proximal jejunum and the distal colon in a single infant with cows' milk protein sensitive enteropathy challenged with oral cows' milk protein.[5] This observation suggested that oral challenge with the protein may evoke morphological changes not only in the jejunum but also in the rectum in infants sensitive to food proteins.

The present study was undertaken to obtain further data on changes in the rectal mucosa and changes in the proximal jejunal mucosa in infants who were allergic to milk.

Patients and methods

Eleven infants (six boys and five girls) who presented with diarrhoeal disease were studied. Eight of them had had diarrhoea for more than seven days and three had recurrent bouts of diarrhoea over a six week period with poor weight gain before admission. After correction of fluid and electrolyte imbalances,[14 15] the infants were given a lactose free cows' milk formula (AL 110, Nestlé) but these infants failed to improve after 48 hours. Moreover, only four of them had pathogens in their stools. Thus it was suspected clinically that the diarrhoeal disease was caused by intolerance to cows' milk protein and so the infants were first given a formula free of cows' milk protein—such as Pregestimil (Mead Johnson), Nutramigen (Mead Johnson), or Alfare (Nestlé)—and then further tests were carried out.[16] All infants were kept in hospital until the stools were normal, they were feeding well, and gaining weight. They were then discharged home. The mothers were supplied with the appropriate formulas and instructed not to offer any other milk without consulting us. Six weeks later the infants were readmitted for further study.

COWS' MILK PROTEIN CHALLENGE TEST

The infants were diagnosed as having cows' milk protein sensitive enteropathy on the criteria outlined previously based on cows' milk protein challenge studies.[1 3] In brief, the test consisted of an initial feed of 5 ml of a low lactose cows' milk formula (AL 110, Nestlé). If no reaction occurred the volume was doubled hourly for the first four hours, and subsequently every three hours, until daily requirements were met. If the infants developed severe symptoms the challenge was terminated and the infant placed on an oral rehydrating solution and then a protein hydrolysate formula.

JEJUNAL BIOPSY AND RECTAL BIOPSY

Jejunal and rectal biopsies were carried out after informed consent was obtained from the parents. Biopsy specimen were taken before challenge and then again 20–24 hours after the introduction of the provocation formula, irrespective of the development of symptoms. The proximal jejunal biopsy specimen was taken through the mouth with the Watson paediatric capsule placed at, or just distal to, the duodenal-jejunal flexure. The specimen was then examined under a dissecting microscope. A portion of the specimen was sent for histological examination, and the remainder for enzyme assay or other studies.

Appearances of the jejunal biopsy specimen were classified according to: (i) villous morphological appearance under the dissecting microscope, (ii) villus:crypt height ratio, (iii) epithelial cells, and (iv) the degree of cellular infiltration. The morphological changes in the mucosa were scored by our modification[1 3] of the method of Townley *et al.*[17]

The rectal biopsy specimen was taken with a Watson paediatric capsule 7–10 cm from the anus. A portion of the tissue was sent for histological examination and the remainder for enzyme assay. The main histological features noted were (i) morphological changes, necrosis, and degeneration of the epithelial cells; (ii) the degree of inflammatory infiltration of the epithelial layer; (iii) the density of the inflammatory cells within the lamina propria; and (iv) signs of degeneration and necrosis in the crypts and glandular cells.

ASSAY FOR ALKALINE PHOSPHATASE

Biopsy specimens, frozen at −20°C for no longer than two weeks, were used for the assay. Alkaline phosphatase and protein estimation on the tissue were carried out as described previously.[18]

OTHER INVESTIGATIONS

Attempts were made to isolate parasitic, bacterial, and viral pathogens from the stools by culture, and by light and electron microscopy. In addition, a mucosal imprint was taken routinely to detect *Giardia lamblia* by the method of Kamath and Murugasu.[19] Testing of stools by the Clinitest method[20] to detect secondary sugar intolerance was carried out at initial illness and after cows' milk protein challenge if diarrhoea occurred.

STATISTICAL ANALYSIS

The changes in the alkaline phosphatase activities (IU/g protein) between the two sets of biopsy specimens of the jejunal and rectal mucosa were analysed by the paired Student's *t* test corrected for small sample size.

Results

Two Malay infants, four Chinese, and five Indians were studied. One infant was breast fed for a month, two had had bottle and breast feeds for a month, and the remaining eight had been bottle fed from birth.

At admission all 11 infants had diarrhoea, and other symptoms included vomiting (n=4), fever (n=4), anal excoriation (n=8), and abdominal distension (n=1). Sugar intolerance (positive Clinitest) was present in all the infants.

Salmonella spp and *Escherichia coli* were each isolated from the stools of one infant, and rotavirus from two infants. The stools from the remaining infants did not grow any bacterial, viral (rotavirus), or parasitic enteric pathogens. The clinical features of the infants are summarised in table 1.

At readmission, after a six to eight week period of receiving a protein hydrolysate formula, all the infants were clinically well and had gained weight satisfactorily. In none did the stools grow any enteric pathogens.

CHALLENGE STUDIES

On the basis of the clinical response to challenge with cows' milk protein the infants were divided into two groups.

Group 1 comprised six infants who developed symptoms of diarrhoea, vomiting, fever, lethargy,

Table 1 *Clinical features in 11 infants with diarrhoea. Figures are expressed as median (range).*

Age at admission (days)	120 (21–510)
Age at onset of diarrhoea (days)	113 (14–495)
Duration of diarrhoea (days)	7 (2–21)

and weight loss. The symptoms occurred between two and 24 hours in four, and two to 14 days in the other two. In four of these six infants the jejunal mucosa after challenge had demonstrable morphological changes associated with significant ($p<0·01$) depletion of the mucosal alkaline phosphatase activities (table 2). Two infants, however, one with symptoms at 48 hours and the other after 14 days, did not show morphological changes in the jejunal mucosa 24 hours after the challenge. Interestingly, in one of these two infants the mucosal alkaline phosphatase activity after challenge was considerably increased over that before the challenge. A repeat biopsy in the latter infant, however, three days after the challenge (while still on cows' milk) and 24 hours after clinical symptoms had appeared, showed severe morphological changes in the jejunal mucosa; these were also associated with severe depletion of the mucosal alkaline phosphatase activity. A repeat biopsy in the other infant was not done. The rectal mucosa after challenge in all six infants had severe morphological changes associated with significant

Table 2 *Changes in the histological condition and alkaline phosphatase content of jejunal and rectal mucosa in six infants who reacted to challenge with cows' milk protein (group 1)*

	Case Nos						*Mean (SD)*	*P Value*
	1	*2*	*3*	*4*	*5*	*6*		
Duration of symptoms (hours)	2 hours	10 hours	60 hours	42 hours	48 hours	14 days		
Jejunal mucosa								
Histological score[13]								
Before challenge	0	0	3	2	0	0	0·8 (1·3)	<0·01
24 Hours after challenge	13	10	12	10	2	2	8·2 (4·9)	
Alkaline phosphatase (IU/g protein)								
Before challenge	168·0	140·0	124·0	111·4	86·3	108·0	123·0 (28·4)	<0·01
24 Hours after challenge	19·0	32·0	92·4	34·6	129·2	88·9	66·0 (43·7)	
Change (%)	−88·7	−77·1	−25·5	−68·9	+49·5	−17·7	−46·3	
Rectal mucosa*								
Alkaline phosphatase (IU/g protein)								
Before challenge	30·5	14·5	25·4	12·1	9·5	23·1	18·4 (7·9)	<0·01
24 Hours after challenge	4·9	2·2	5·6	6·1	1·4	1·8	3·6 (1·9)	
Change (%)	−83·9	−84·8	−78·0	−49·6	−85·3	−92·2	−80·7	

*Histological appearances in all cases were normal before challenge and showed evidence of damage after challenge.

Table 3 *Changes in the histological condition and alkaline phosphatase content of jejunal and rectal mucosa in five infants who did not react to challenge with cows' milk protein (group 2)*

	Case Nos					*Mean (SD)*	*P Value*
	1	*2*	*3*	*4*	*5*		
Jejunal mucosa							
Histological score[13]							
Before challenge	3	2	2	0	0	1·4 (1·3)	>0·05
24 Hours after challenge	3	3	4	2	2	2·8 (0·7)	
Alkaline phosphatase (IU/g protein)							
Before challenge	52·1	88·6	45·9	167·5	120·0	94·8 (45·8)	
24 Hours after challenge	178·7	78·5	201·5	145·2	128·0	146·4 (47·5)	0·8
Change (%)	+243·0	−11·4	+339·8	−13·3	+6·7	+54·4	
Rectal mucosa*							
Alkaline phosphatase (IU/g protein)							
Before challenge	4·9	15·0	3·7	12·6	8·4	8·9 (4·8)	
24 Hours after challenge	13·6	22·0	4·2	8·3	7·0	11·0 (7·0)	0·6
Change (%)	+177·6	+46·7	+13·5	−34·1	−16·7	+23·6	

*Histological appearances were normal both before and after challenge.

($p<0.01$) depletion in mucosal alkaline phosphatase activities.

Five of the six reactive infants (early and delayed) required hypoallergenic milk substitutes to recover. The sixth infant (case 5, table 2) had diarrhoea with perianal excoriation for three days but improved spontaneously despite continued feeding with cows' milk protein. He was not available for further biopsy studies.

Group 2 comprised five infants who did not react to the challenge with cows' milk protein. The rectal mucosa in these infants showed no change. The alkaline phosphatase activities after challenge were increased in the jejunal biopsy specimen in two infants, and in the rectal biopsy specimen in three infants (table 3).

HISTOLOGICAL FEATURES OF RECTAL BIOPSY SPECIMENS

The architecture of the rectal mucosa before challenge with cows' milk was normal and there was no evidence of crypt branching, atrophy, or dense inflammatory cell infiltration of the lamina propria.

The rectal mucosa after challenge in the six infants who reacted to the cows' milk protein showed several abnormal features: cuboidal metaplasia with loss of polarity of the nuclei of the epithelial cells; increased infiltration of the epithelium with lymphocytes; necrosis of the surface epithelial cells; infiltration of the lamina propria with inflammatory cells (lymphocytes, plasma cells, monocytes, and eosinophils); necrosis of the crypts and glandular cells; and variable degrees of mucin depletion in the glandular cells.

Discussion

Our criteria for the diagnosis of cows' milk protein sensitive enteropathy are based on the morphological changes of the jejunal mucosa and development of clinical symptoms within 24 hours of challenge with cows' milk protein.[11] Using these criteria only four of the 11 infants in the present series were diagnosed as having cows' milk protein sensitive enteropathy; the other seven infants were considered not to have it. In two of the latter seven infants, however, though the oral challenge induced no jejunal abnormality, symptoms appeared two to 14 days after challenge with cows' milk protein. These two infants with delayed reactions would not have been classified as having cows' milk protein sensitive enteropathy by our criteria because the jejunal biopsy was unchanged 24 hours after challenge with cows' milk protein. In one of the two infants, a follow up biopsy obtained three days after the challenge, indicated mucosal injury, but the other infant was not subsequently biopsied. Nevertheless an interesting feature of all the reactive infants, both early and delayed, was the development of rectal mucosal lesions associated with depletion of mucosal alkaline phosphatase activity.

The rectal mucosal abnormality appeared within 24 hours of initiating the oral milk challenge, which strongly suggests that the cows' milk proteins were directly responsible for the response. In some the rectal changes may have been caused by the diarrhoea, which could have brought toxic products from the upper gut to the colon and rectum, but in two cases this was not so because colonic changes occurred in the absence of jejunal changes. Moreover, none of the five unreactive infants had similiar lesions in the rectal mucosa. These observations suggest that the ingested food proteins could cause damage to the distal colon independently of the proximal small gut. The pathogenetic mechanisms responsible for the rectal mucosal injury remain unclear, but the increased infiltration with mononuclear cells and eosinophils suggests an immune associated injury. Although colitis and proctitis specifically induced by milk proteins are well known in children,[21–24] their association with gastroenteritis remains uncertain.

The severe proctitis in the two infants who did not have any injury to the proximal jejunum is an unexpected but interesting finding. In both the infants symptoms were delayed. Goldman and Proujansky in their study of 53 infants with allergic gastroenteropathy observed that of 15 cases of allergic proctitis, all but one had lesions limited to the rectum and colon.[13] These, together with our present observations, are contrary to previous reports in which severity of mucosal damage caused by gluten or cows' milk protein, were noted to decrease in severity craniocaudally. We noted that mucosal disaccharidases and alkaline phosphatase activities were depleted in both the proximal and distal jejunal biopsy specimen after challenge with cows' milk but the enzyme depletion was greater in the proximal than in the distal biopsy specimens.[5] This craniocaudal decrease in severity of mucosal damage was more obvious in reactive infants who had only mucosal injury compared with reactive infants who had both mucosal injury and symptoms. In the latter group the mucosal response was more widespread, and in one case lesions were also noted in the rectal mucosa.

Grybowski has shown that the rectal mucosa was damaged and there were clinical features of enterocolitis in eight infants sensitive to cows' milk protein.[22] Taken together it appears that the entire gut is potentially sensitive to cows' milk protein in cows' milk protein sensitive enteropathy. The extent and severity of damage to the mucosa after challenge with cows' milk protein in reactive infants depend on several opposing sets of factors, with competency of the immunodigestive system and other protective barriers of the mucosa on one side, and the quantity and immunogenecity of cows' milk protein and other adverse factors (such as enteric infection and age of infant) on the other. Thus the clinical and pathogenetic responses may be part of a broad range of reactions in which the site, nature, severity, and extent of damage will depend on the spread of the protein and the nature of the infant's immune response.

In clincial practice the management of infants with chronic diarrhoea requires the need to establish whether the illness is caused by intolerance of food protein. Although jejunal biopsy through the mouth has been the preferred method of diagnosis, it has the disadvantage of requiring expensive equipment and skilful intubation. By contrast, rectal biopsy may be obtained quickly with little equipment and could be the alternative option when jejunal biopsy is not possible. This study shows that the changes in rectal mucosa before and after challenge with oral cows' milk protein predicted intolerance to cows' milk in the infants studied.

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References

[1] Iyngkaran N, Robinson MJ, Prathap K, Sumithran E, Yadav M. Cows' milk protein-sensitive enteropathy: combined clinical and histological criteria for diagnosis. *Arch Dis Child* 1978;**53:** 20–6.

[2] Iyngkaran N, Abidin Z, Meng LL, Yadav M. Egg-protein induced villous atrophy. *J Pediatr Gastroenterol Nutr* 1982;**1:** 29–34.

[3] Iyngkaran N, Yadav M, Looi LM, Boey CG, Lam KL, Balabaskaran S, Puthucheary SD. Effect of soy protein on the small bowel mucosa of young infants recovering from acute gastroenteritis. *J Pediatr Gastroenterol Nutr* 1988;**7:**68–75.

[4] Walker WA, Isselbacher KJ. Uptake and transport of macromolecules by the intestine. Possible role in clinical disorders. *Gastroneterology* 1974;**67:**531–50.

[5] Iyngkaran N, Yadav M, Boey CG, Lam KL. Severity and extent of upper small bowel mucosal damage in cows' milk protein-sensitive enteropathy. *J Pediatr Gastroenterol Nutr* 1988;**7:** 667–74.

[6] Stokes CR, Soothill JF, Turner MW. Immune exclusion is a function of IgA. *Nature* 1975;**255:**765–6.

[7] Walker WA, Isselbacher KJ. Intestinal antibodies. *N Engl J Med* 1977;**267:**767–9.

[8] Yadav M, Iyngkaran N. Immunological studies in cows' milk protein-sensitive enteropathy. *Arch Dis Child* 1981;**56:**24–30.

[9] Carini C. IgE immune complexes in food allergy: significance, pathogenicity and clinical considerations. *Clin Allergy* 1987;**17:** 485–97.

[10] Ferguson A, McClure JP, Townley RRW. Intraepithelial lymphocyte counts in small intestinal biopsies from children with diarrhoea. *Acta Paediatr Scand* 1976;**65:**541–7.

[11] Kumate J, Isibasi A. Pediatric diarrhoeal diseases: a global perspective. *Pediatr Infect Dis* 1986;**5:**521–8.

[12] Iyngkaran N, Yadav M. Food alltergy In: Marsh MN, ed. *Immunopathology of small intestine.* Chichester: John Wiley, 1987:415–49.

[13] Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 1986;**10:**75–86.

[14] Iyngkaran N, Zainal A, Lam SK, Puthucheary SD. Acute gastroenteritis in Malaysian children aetiological and therapeutic considerations. *Med J Malaysia* 1980;**34:**403–8.

[15] Zainal A, Iyngkaran N, Geethan R. Oral rehydration in infantile diarrhoea. The optimum carbohydrate-electrolyte composition. *J Singapore Paediatr Soc* 1980;**20:**100–3.

[16] Iyngkaran N, Zainal A, Robinson MJ, Yadav M, Boey CG, Chai KH. Nutritional rehabilitation of infants with protracted diarrhoea: comparative study of three therapeutic regimen. *Asean Journal of Clinical Science* 1982;**3:**160–6.

[17] Townley RRW, Khaw KT, Shwachman H. Quantitative assay of dissacharidase activities of small intestinal mucosal biopsy specimens in infancy and childhood. *Pediatrics* 1965;**36:**911–21.

[18] Iyngkaran N, Yadav M, Balabaskaran S, Sumithran E. In vitro diagnosis of cows' milk protein sensitive enteropathy by organ culture method. *Gut* 1981;**22:**199–202.

[19] Kamath KR, Murugasu R. A comparative study of four methods for detecting Giardia lamblia in children with diarrhoeal disease and malabsorption. *Gastroenterology* 1974;**66:**16–21.

[20] Kerry ER, Anderson CM. A ward test for sugar in the faeces. *Lancet* 1964;**i:**981.

[21] Ament M, Rubin CE. Soy protein–another cause of the flat intestinal lesion. *Gastroenterology* 1972;**62:**227–34.

[22] Grybowski JD. Gastrointestinal milk allergy in infants. *Pediatrics* 1967;**40:**354–60.

[23] Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harrier JJ. Food allergy: the major cause of infantile colitis. *Arch Dis Child* 1984;**59:**326–9.

[24] Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine* 1970;**49:**229–319.

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Which routine test for kidney function?

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SUMMARY Eighty measurements of plasma creatinine concentration, height:creatinine ratio, and plasma β_2 microglobulin concentration were made on 72 children (age 4 months–18·5 years) with known renal disease. Results were compared with simultaneous measurements of glomerular filtration rate using plasma clearance of ^{51}Cr edetic acid to assess the performance of each test as an initial screening procedure of renal insufficiency. Height:creatinine index <2·1 was found to have a higher sensitivity and predictive value of a normal result than the other tests and is therefore the preferred test for a screening procedure.

A simple reliable method of measuring glomerular filtration rate is important in the routine assessment of children with renal disease. The creatinine clearance test is inherently inaccurate with poor reproducibility.[1] Radionuclide clearance methods are more accurate but available only in specialised centres. Therefore, the plasma creatinine alone is used in the routine assessment of glomerular filtration rate. In children, as plasma creatinine concentration changes with age, correction is made for changes due to growth by calculating a height:creatinine index, which has some advantages.[2]

There is an inverse relationship between plasma β_2 microglobulin concentration and glomerular filtration rate and it has been suggested that this is used to measure glomerular filtration rate.[3] In contrast with creatinine its plasma concentration is unaffected by diet[1] but its production is enhanced by active infection or malignancy.

The aim of this study was to compare the sensitivities and predictive values of plasma concentration, height:creatinine index, and plasma β_2 microglobulin as methods of assesssing glomerular filtration rate using plasma clearance of ^{51}Cr edetic acid as a 'gold standard' so that recommendations can be made to the non-nephrologist for the test that is most helpful for routine clinical use.

Patients and methods

Seventy two children known to have renal disease were studied. There were 33 girls and 39 boys aged between 4 months and 18·5 years. Four of these children had two measurements and a further two had three measurements after intervals of several months making 80 observations in total. All the children were weighed, their heights measured using a Harpenden stadiometer, and their surface areas calculated using the Dubois formula.[4] Fasting plasma creatinine concentration was measured by a kinetic Jaffe reaction using a Rank Elger Chemspeck autoanalyser. The β_2 microglobulin was measured by radioimmunoassay (Phadebas (R) B2 microtest, Pharmacia Diagnostics). Sera were stored at −20°C before analysis.

Glomerular filtration rate was calculated from the plasma clearance of ^{51}Cr edetic acid using standard methods.[5] Results were corrected to 1·73 m^2 body surface area before analysis.

Impaired renal function was defined as a plasma clearance of ^{51}Cr edetic acid of less than 80 ml/min/1·73 m^2 in children over 3 years. In those under 3 years when normally glomerular filtration rate changes with age, renal impairment was defined as clearance more than two standard deviations below the published mean for age.[6]

Normal plasma creatinine concentration has a log normal distribution.[1] All analysis were therefore performed after logarithmic transformation and standard statistical methods were applied.

Results

The mean coefficient of variation of the creatinine measurement at a plasma concentration of 70 μmol/l was 8% and of β_2 microglobulin was 6% on both repeated measurements of the same sample and repeated samples from the same patient. The

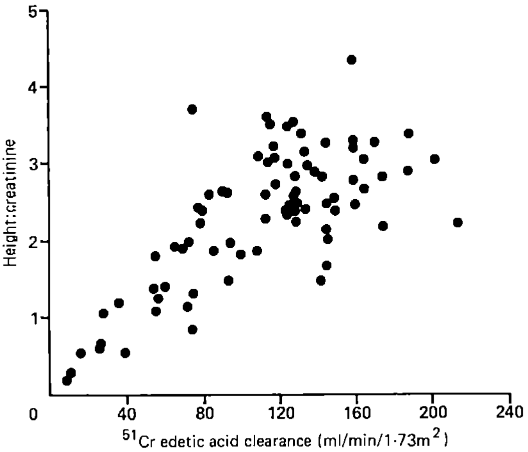

Figure *Distribution of height:creatinine and clearance of ^{51}Cr edetic acid in all patients.*

reproducibility of the plasma clearance of ^{51}Cr edetic acid in six healthy adults was 4%.

The plasma clearance of ^{51}Cr edetic acid was greater than 80 ml/min/1·73 m^2 in 58 measurements (mean (SD) 140 (28)). There was a linear relationship between plasma clearance of ^{51}Cr edetic acid and 1/creatinine, 1/β_2 microglobulin, and height: creatinine index with correlation coefficients of 0·88, 0·87, and 0·85 respectively. The distribution of plasma clearance of ^{51}Cr edetic acid and height: creatinine index for the patients studied is shown in the figure. The geometric means and ranges of plasma creatinine and β_2 microglobulin of patients with normal plasma clearance of ^{51}Cr edetic acid are shown in table 1. Age had a greater effect on creatinine than β_2 microglobulin. Sex had no effect on the plasma β_2 microglobulin concentrations at any age and the results of boys and girls were combined. A sex difference was observed between plasma creatinine concentration of boys and girls over 12 years.

Twenty two of the 80 observations showed abnormal clearance (range 10–77, mean (SD) 50 (25) ml/min/1·73 m^2).

It has been suggested that the height:creatinine index can be used to predict glomerular filtration rate; and index of less than 1·5 corresponding to a glomerular filtration rate less than 80 ml/min/1·73 m^2 and greater than 2·1 predicting a glomerular filtration rate greater than 80 ml/min/1·73 m^2.[2]

Table 2 shows details of the results of the four tests considered. Plasma creatinine and β_2 microglobulin were considered abnormal if they were greater than the normal range in table 1. From these the sensitivities, specificities, and predictive values were calculated and are shown in table 3.

Table 2 *Test results compared with plasma clearance of ^{51}Cr edetic acid*

	Test result	*Plasma clearance of ^{51}Cr edetic acid*	
		>80 ml/min	*<80 ml/min*
β_2 microglobulin	–	57	7
	+	1	15
Creatinine	–	55	8
	+	3	14
Height:creatinine <2·1	–	46	2
	+	12	20
Height:creatinine	–	57	7
	+	1	15

Table 1 *Plasma creatinine and β_2 microglobulin concentrations in children with a plasma clearance of ^{51}Cr edetic acid greater than 80 ml/min/1·73 m^2*

Age (years)	*No of children*		*β_2 microglobulin (g/l)*		*Creatinine (µmol/l)*	
	Boys	*Girls*	*Geometrical mean*	*Range*	*Geometrical mean*	*Range*
0·3–2·9	2	6	2415*	1306–4467	32·9*	15·0–73·0
3·0–7·9	8	6	2070	1462–2931	47·0*	34·9–63·2
8·0–11·9	9	9	1745	1067–2885	53·2	33·0–85·8
12+	12	6	1584	896–2802	58·8	39·5–87·4
Boys					66·0	44·3–98·2
Girls					48·0	42·0–54·9

*Significant difference from mean 12+ age group.

Table 3 *Sensitivity, specificity, and predictive values of renal function tests. Results are percentages*

Test	*Sensitivity*	*Specificity*	*Predictive value of abnormal result*	*Predictive value of normal result*
Creatinine >2 SD	64	95	82	87
β_2 microglobulin	68	98	94	89
Height:creatinine <2·1	91	79	63	96
Height:creatinine <1·5	68	98	94	89

Discussion

In a situation where no single test has clear advantages in terms of sensitivity and specificity, the relative importance of each must be considered. Table 3 shows that the sensitivity of height:creatinine index <2·1 is higher than the other tests but its specificity is inferior.

Failure to detect reduced glomerular filtration rate in a child could result in progression of disease, further deteriorating renal function, and irreversible damage. Conversely, the consequence of a false diagnosis of reduced glomerular filtration rate is that the patient will be referred for unnecessary additional investigations. A preliminary screening test must therefore, above all else, have a high sensitivity and a high predictive value of a normal test.

Plasma creatinine corrected for age and sex was more specific than height:creatinine index <2·1 but its sensitivity was inferior. Similarly, height: creatinine index <1·5 and β_2 microglobulin had high specificity but lower sensitivity. In addition, the higher cost and more complex assay procedure required for β_2 microglobulin limit its usefulness as a screening test in routine clinical practise.

The test with clear advantages of higher sensitivity and higher predictive value of a normal result was height:creatinine index <2·1.

References

[1] Payne RB. Creatinine clearance: a redundant clinical investigation. *Ann Clin Biochem* 1986;**23**:243–50.

[2] Morris MC, Allanby CW, Toseland P, Haycock GB, Chantler C. Evaluation of a height/plasma creatinine formula in the measurement of glomerular filtration rate. *Arch Dis Child* 1982;**57**:611–5.

[3] Wibell L, Evrin PE, Berggard I. Serum beta 2 microglobulin in renal disease. *Nephron* 1973;**10**:320–31.

[4] Dubois D, Dubois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916;**17**:863–71.

[5] Chantler C, Barratt TM. Estimation of glomerular filtration rate from plasma clearance of 51 chromium edetic acid. *Arch Dis Child* 1972;**47**:613–7.

[6] Winberg J. The 24-hour true creatinine clearance in infants and children without renal disease. *Acta Paediatrica* 1959;**48**:443–52.

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Neonatal renal function assessment

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SUMMARY Urine samples from neonates admitted to a special care baby unit were analysed to establish ranges for urinary retinol binding protein, albumin, and total protein concentrations in healthy term and preterm infants and to investigate changes seen in disease states. Urinary excretion of retinol binding protein was greater in preterm infants and was increased in sick infants. This was greater than would be predicted from changes in creatinine excretion with gestational or postconceptional age. Urinary retinol binding protein appeared more sensitive to illness than did urinary albumin or total protein.

The measurement of renal function in neonates is not easy: it is difficult to obtain timed urine specimens and blood sampling requires skill. Biochemical techniques that could be performed on untimed urine samples to predict changes in renal function would therefore be useful. In addition, current sensitive and specific techniques to measure individual proteins can now be used to differentiate between glomerular and tubular dysfunction.

The increased excretion of albumin in urine, before dipstick methods or routine laboratory total protein methods showed abnormal results, was used to predict glomerular damage and later renal failure in diabetic patients.[1 2] Other studies have shown that plasma proteins with molecular weights less than 30 000 daltons (for example, retinol binding protein and β_2 microglobulin) are freely filtered at the glomerulus and reabsorbed at the proximal renal tubule.[3] Their reabsorption is normally quantitative and therefore increased excretion of these proteins may indicate renal tubular damage. β_2 microglobulin has been used in the past to assess renal tubular function and has been measured in infants born through meconium stained liquor.[4] There are no reports of urinary retinol binding protein excretion in healthy and sick neonates.

Retinol binding protein is now known to be more stable in normal acid urine than is β_2 microglobulin and should therefore be a preferred indicator of tubular function.[5] Measurement of albumin concentrations should give a measure of glomerular function.

The degree of renal function in utero and in the neonatal period is affected by the gestational age of the infant and by factors such as infection and concomitant treatment with antibiotics. Renal function should therefore be monitored during the treatment of infection to minimise adverse affects on renal function and if possible to give early warning of impending renal damage. Such investigations are complicated by changes in renal function with degree of prematurity.

In this study the urinary excretion of retinol binding protein, albumin, and total protein were measured to establish their normal ranges in healthy term and preterm babies and to investigate the effects of prematurity, illness, and antibiotic drug treatment on their excretion.

Patients and methods

Samples were collected from 221 babies admitted to the special care baby unit between October 1985 and June 1986. Babies were excluded from the study if they were known to have specific renal pathology, for example a congenital malformation or renal venous thrombosis. Information on gestation, birth weight, requirement for increased inspired oxygen concentration, need for ventilation, presence of jaundice requiring phototherapy, administration of antibiotics, and feeding (milk, intravenous glucose, or total parenteral nutrition) was collected on all babies. This information was used to divide the subjects into three groups: 'well', 'special care' and 'intensive care'. The well babies were not given antibiotics, did not need ventilation, and were fed on milk. The special care babies received intravenous dextrose with or without parenteral antibiotics. The intensive care babies required antibiotics, total parenteral nutrition, and some also required ventilation.

The antibiotics used were cefotaxime alone (48 babies) or netilmicin and benzylpenicillin in combination (42 babies). Eighteen babies received netilmicin alone and 21 received benzylpenicillin and cefotaxime together. It was hoped that the study would show up any differences in renal toxicity between these antibiotic regimes.

The babies who were given antibiotics had all had an infection screen performed. The results of this, which included blood culture, urine culture, surface swabs, erythrocyte sedimentation rate, C reactive protein, and white cell count with differential count, were used to decide whether sepsis was present.[6]

Table 1 *Gestation and health of subjects*

	Gestation (weeks)			*Total*
	<30	*30–36*	*>36 (term)*	
Group:				
Well	0	31	25	56
Special care	9	59	58	126
Intensive care	22	13	4	39
Total	31	103	87	221

Untimed urine specimens were collected in a bag applied to the perineum and stored frozen at −20°C until their analysis. Specimens contaminated with faeces were discarded. Most specimens (60·9%) were collected during the first 2 days of life, with a few (12·9%) being collected from babies over 1 week of age. Only the results from the first sample from each baby were included in the statistical analysis.

Blood samples were only taken for assessment of renal function where the clinical condition of the baby merited it; therefore the results for plasma urea and creatinine are incomplete. Plasma urea and creatinine were measured by routine biochemical techniques. Urinary retinol binding protein was measured by radioimmunoassay.[7] The coefficient of variations of the method were approximately 6% for quality control samples with concentrations between 20 and 500 μg/l.

Table 2 *Plasma urea and plasma and urinary creatinine. Results for plasma urea and plasma creatinine are means (numbers of babies) and differences between means with 95% confidence intervals. Results for urinary creatinine are geometric means (numbers of babies) and ratios with 95% confidence intervals*

	Gestation (weeks)		
	<30	*30–36*	*>36*
Plasma urea (mmol/l):			
Well	—	3·32 (17)	4·05 (14)
Special care	4·57 (9)	3·97 (46)	3·20 (44)
Intensive care	4·76 (21)	3·38 (13)	6·97 (4)
Special care−well	—	0·65 (−0·32 to 1·62)	−0·85 (−2·24 to 0·53)
Intensive care−well	—	0·07 (−1·26 to 1·39)	2·92 (−0·8 to 6·60)
Intensive care−special care	0·19 (−2·51 to 2·12)	−0·58 (−1·82 to 0·66)	3·78 (0·0 to 7·58)
Plasma creatinine (μmol/l):			
Well	—	83·2 (4)	58·5 (6)
Special care	88·1 (9)	76·8 (34)	70·1 (22)
Intensive care	86·2 (15)	70·3 (7)	134·0 (2)
Special care−well	—	−6·43 (−29·3 to 16·5)	11·6 (−11·8 to 35·0)
Intensive care−well	—	−12·9 (−34·9 to 8·9)	75·5 (−520 to 670·8)
Intensive care−special care	−1·91 (−19·7 to 23·5)	−6·54 (−18·7 to 5·6)	63·9 (−524 to 651·6)
Urinary creatinine (mmol/l):			
Well	—	1·61 (31)	2·67 (25)
Special care	1·07 (9)	1·61 (59)	2·32 (58)
Intensive care	1·02 (22)	1·52 (13)	5·33 (4)
Special care−well	—	1·00 (0·72 to 1·39)	0·87 (0·54 to 1·39)
Intensive care−well	—	0·95 (0·58 to 1·54)	2·00 (0·69 to 5·76)
Intensive care−special care	0·95 (0·55 to 1·65)	0·94 (0·60 to 1·48)	2·30 (0·83 to 6·35)

Urinary total protein was measured by turbidimetry using benzethonium chloride precipitation.[8] Urine albumin was measured by immunoturbidimetry on an LKB 8086 reaction rate analyser.[9] The coefficient of variation of the method was 10% at 30 mg/l. Urinary creatinine was measured by a pseudo kinetic modification of the Jaffé method.

Data were analysed using the Statistical Package for the Social Sciences x (release 2.2) and Minitab (revision 5.1.3). Results of urinary proteins were expressed as ratios to the urinary creatinine concentration to correct for differences in urine flow rate. These urinary protein:creatinine ratios exhibited a skewed distribution and were $\log_{10}$ transformed for analysis. No attempt was made to relate creatinine excretion to body surface area. Significance was tested using analysis of variance, differences between groups were tested using the least significant difference test at the 1% level. The effects of combinations of variables were investigated using multiple regression analysis.

Results

Two of the 129 babies given antibiotics had sepsis as shown by positive blood cultures; a further 43 were probably infected as shown by other indicators of infection such as a raised C reactive protein, white cell count, or erythrocyte sedimentation rate.

The distribution of gestational age at birth is shown in table 1. None of the infants of less than 30 weeks' gestation at birth were considered healthy; this is to be expected as over 50% of babies of this gestational age would develop respiratory distress syndrome and require supportive treatment.[10] Tables 2 and 3 summarise the plasma and urine results. Urinary creatinine results were within the range described by Sertel and Scopes, who studied a population of well, term babies.[1]

In the three gestational age groups there were trends towards higher levels of albumin:creatinine, retinol binding protein:creatinine, and total protein: creatinine excretion ratios with increasing degrees of

Table 3 *Urinary albumin, retinol binding protein, and total protein: creatinine ratios. Results are geometric means (numbers of babies) and ratios with 95% confidence intervals*

	Gestation (weeks)		
	<30	*30–36*	*>36*
Urinary albumin:creatinine (mg:mmol):			
Well	—	21·3 (31)	11·9 (25)
Special care	26·2 (9)	18·4 (59)	13·8 (57)
Intensive care	36·4 (22)	21·1 (13)	58·7 (4)
Special care–well	—	0·86 (0·82 to 0·90)	1·17 (0·70 to 1·96)
Intensive care–well	—	0·99 (0·92 to 1·06)	4·97* (1·55 to 15·9)
Intensive care–special care	1·39 (1·09 to 1·76)	1·15 (1·08 to 1·23)	4·26 (1·40 to 13·0)
Urinary retinol binding protein:creatinine (μg:mmol)			
Well	—	251·2 (31)	39·4 (25)
Special care	1845·0 (9)	365·9 (59)	123·3 (55)
Intensive care	2454·7 (21)	727·8 (13)	1849·2 (4)
Special care–well	—	1·46 (0·68 to 3·14)	3·13* (1·38 to 7·07)
Intensive care–well	—	2·90 (0·92 to 9·10)	46·94* (7·60 to 289·8)
Intensive care–special care	1·33 (0·87 to 2·05)	1·99 (0·69 to 5·75)	15·00* (6·06 to 37·14)
Urinary total protein:creatinine (mg:mmol):			
Well	—	200·9 (31)	108·3 (25)
Special care	312·0 (9)	193·9 (58)	137·0 (56)
Intensive care	315·6 (22)	204·3 (13)	368·1 (3)
Special care–well	—	0·97 (0·74 to 1·26)	1·27 (0·98 to 1·63)
Intensive care–well	—	1·02 (0·68 to 1·52)	3·40* (1·79 to 6·47)
Intensive care–special care	1·01 (0·89 to 1·15)	1·05 (0·87 to 1·27)	2·69* (1·86 to 3·89)

illness (see table 3); these changes were significant in the term (greater than 36 weeks) babies. The differences between the well, special care, and intensive care groups that were significant are shown in table 3. Only the well and intensive care groups could be distinguished for urinary albumin:creatinine ratios, whereas all groups were different for the retinol binding protein:creatinine ratio. The well and special care groups were different from the intensive care group but were not different from each other for the total protein:creatinine ratio. The increases in the term babies were larger than those in the 30–36 week gestation group.

Multiple regression analysis did not show any significant effects due to antibiotic administration or to the choice of antibiotic used.

The association between urinary retinol binding protein and urinary albumin:creatinine ratios for all babies gave a correlation coefficient of 0·58 ($p<0{\cdot}001$). This only accounts for a 35% agreement between these two measurements, however, and is consistent with their indicating different aspects of renal function.

It can be seen from table 3 that the well, term babies had lower values for urinary retinol binding protein:creatinine, albumin:creatinine, and total protein:creatinine ratios when compared with the well babies of the 30–36 week gestation group. These differences were significant for the retinol binding protein:creatinine and total protein:creatinine ratios ($p<0{\cdot}001$).

Table 4 summarises the results for well babies of 30–36 weeks and over 36 weeks' gestation. It can be seen that the well babies of over 36 weeks' gestation had lower values for urinary retinol binding protein: creatinine, albumin:creatinine and total protein: creatinine ratios when compared with the well babies of the 30–36 week gestation group. These differences were significant for the urinary retinol binding protein:creatinine and total protein: creatinine ratios ($p<0{\cdot}001$).

Table 4 *Normal ranges for well babies. Results are geometric mean and mean (1·96 SD)*

	Gestation (weeks)	
	30–36	*>36*
Urinary albumin: creatinine (mg:mmol)	21·3, 1·32 (343·8)	11·9, 1·78 (78·63)
Urinary retinol binding protein: creatinine (μg:mmol)	251·2, 0·50 (19828·0)	39·4, 2·92 (533·2)
Urinary total protein: creatinine (mg:mmol)	200·9, 41·3 (976·8)	108·3, 55·0 (213·2)

Discussion

Retinol binding protein is present in the circulation of the fetus either free or bound to prealbumin. In the preterm infant the plasma retinol binding protein is mainly from maternal sources. It was reported by Ismadi and Olsen that the human fetus does not produce significant amounts of retinol binding protein until about 34 weeks' gestation.[12] Howells *et al* showed that plasma retinol binding protein did not correlate with either gestational age or birth weight.[13] Legge did not find any retinol binding protein in amniotic fluid[14]; however, the assay used was less sensitive than the radioimmunoassay used in this study.

In the well babies (table 4) we have shown a sixfold decrease in urinary retinol binding protein: creatinine ratios and a twofold decrease in urinary total protein:creatinine ratios with the two gestational age groups at birth ($p<0{\cdot}0001$). The urinary albumin:creatinine ratios showed a similar trend but at a lower level ($p<0{\cdot}05$). These results provide tentative reference ranges for the excretion of these proteins in term and preterm neonates.

The changes in renal function with increasing gestation as measured by glomerular filtration rate and plasma creatinine have been shown previously.[15 16] Both these methods require blood sampling to be carried out.

The decrease in the urinary retinol binding protein: creatinine that we have shown may indicate more efficient proximal tubular function as gestation progresses, which would agree with the more efficient glomerular filtration shown by others.[11] The relatively minor changes in the urinary albumin: creatinine ratio with gestation may indicate that this is a less sensitive measure of renal function than tests of proximal tubular function in early life. A protein:creatinine ratio would be expected to decrease with increasing gestational age and skeletal muscle mass (table 2). However, the increase in urinary creatinine appears insufficient to account for the significant decrease in the retinol binding protein:creatinine ratio in the well 30–36 and >36 weeks groups.

Having described reference ranges for urinary retinol binding protein, albumin, and total protein: creatinine ratios, it is now possible to investigate those differences that occur in illness. In this study the sick babies mainly has respiratory illness (either idiopathic respiratory distress syndrome or congenital pneumonia) or generalised septicaemia, although bacteriological confirmation of sepsis was obtained in only two babies. Unsuspected renal tubular dysfunction has been described by Cole *et al* in term babies born through meconium stained liquor[4]; this was detected by measuring β_2 microglobulin in the urine. Increased urinary excretion of small molecular weight proteins may result from competition for reabsorptive sites in the proximal tubule. Such competition may occur from the presence of free branched chain amino acids as are present in intravenous feeding regimes. However, other studies have not shown branched chain amino aciduria in infants on intravenous feeds (V Walker, personal communication).

Plasma creatinine has been used as a measure of renal dysfunction in neonates but, in adults, there is no significant rise until at least 50% of the glomeruli are damaged. It would be useful in the management of fluid and electrolyte balance in neonates to be able to detect renal damage before this degree of loss of function has occurred.

The concentrations of plasma creatinine in all three gestational age groups did not change significantly with severity of illness (table 2), and all lay within the reference ranges described by Rudd *et al.*[17] Thus the measurement of plasma creatinine alone would not have detected any renal dysfunction in the babies studied.

The changes in urinary proteins with increasing severity of illness are most pronounced in the measurement of the retinol binding protein: creatinine ratio in each gestational age group. This suggests that proximal tubular function may be disrupted more than glomerular function in neonatal disease. The increase in the retinol binding protein: creatinine ratio with illness is most noticeable in the over 36 week gestation group—this may be because the well babies of this gestation have relatively mature kidneys, and illness requiring special care is of a more severe nature than in preterm infants who have less general reserve and therefore require more care for less severe illness.

The number of babies in the sick term group was too small (see table 1) to allow the drawing of definite conclusions from the results.

The results in the 30–36 week gestation group show no changes in ratios for urinary albumin: creatinine or total protein:creatinine with varying severity of illness. This probably reflects the overall immaturity of the kidney even in well babies. The urinary retinol binding protein:creatinine ratio does show a trend with severity of illness, but the ranges are such that significance is not reached. However, these results suggest that the urinary retinol binding protein:creatinine ratio may be the most useful for detecting early renal dysfunction in neonates.

In the babies of less than 30 weeks' gestation it is difficult to evaluate the results as there were no normals to compare with the sick babies. However, the results for all variables are generally higher than for more mature babies, again suggesting renal immaturity, especially of the proximal tubule.

This preliminary study indicates that measurement of specific urine proteins may provide sensitive indicators of changes in renal function in neonates either from differences in gestational age or from sickness. Changes in glomerular function appear less dramatic than changes in renal tubular function. The study did not detect differences in renal function related to antibiotic administration but numbers were small. The sensitivity of these non-invasive biochemical markers indicate they may be of use in further studies of renal function in the neonatal period.

References

[1] Mogensen C E, Christensen CK. Predicting diabetic nephropathy in insulin dependent patients. *N Engl J Med* 1984;**311**:89–93.

[2] Viberti GC, Hill RD, Jarrett RJ, *et al.* Microalbuminuria as a predictor of clinical nephropathy in insulin dependent diabetes mellitus. *Lancet* 1982;**i**:1430–2.

[3] Maack T, Johnson V, Khan ST, Figueierdo JF, Sigulem D. Renal function, transport and metabolism of how molecular weight proteins: a review. *Kidney Int* 1979;**16**:251–70.

[4] Cole JW, Portman RJ, Lim Y, Portman JM, Robson AM. Urinary β_2 microglobulin in full-term newborns: evidence for proximal tubular dysfunction in infants with meconium-strained amniotic fluid. *Pediatrics* 1985;**76**:958–63.

[5] Bernard AM, Morean D, Lauwerys R. Comparison of retinol-binding protein and β_2 microglobulin determination in urine for the early detection of tubular proteinuria. *Clin Chim Acta* 1982;**126**:1–7.

[6] Hall MA, Ducker DA, Lowes JA, *et al.* A randomised prospective comparison of cefotaxime versus netilmicin/penicillin for treatment of suspected neonatal sepsis. *Drugs* 1988;**88**: 169–77.

[7] Rowe DJF, Anthony F, Polak A, *et al.* Retinol binding protein as a small molecular weight marker of renal tubular function in diabetes mellitus. *Ann Clin Biochem* 1987;**24**:477–82.

[8] Iwata I, Nishikazi O. New micro tubulidmetric method for determination of protein cerebrospinal fluid and urine. *Clin Chem* 1979;**25**:1317.

[9] Rowe DJF, Hayward M, Bagga H, Betts P. Effect of glycaemic control and duration of disease and overnight albumin excretion in diabetic children. *Br Med J* 1984;**289**:957–9.

[10] Usher RH, Allen AC, McLean FH. Risk of respiratory distress syndrome related to gestational age, route of delivery and maternal diabetes. *Am J Obstet Gynecol* 1971;**111**:826–32.

[11] Sertel H, Scopes J. Rates of creatinine clearance in babies less than one week of age. *Arch Dis Child* 1973;**48**:717–20.

[12] Ismadi SD, Olson JA. Vitamin A transport in human fetal blood. *Am J Clin Nutr* 1975;**28**:967–72.

[13] Howells DW, Levin GE, Brown IRF, Brooke OG. Plasma retinol and retinol-binding protein in pre-term infants born small for gestational age or of appropriate weight for age. *Hum Nutr Clin Nutr* 1984;**38C**:107–11.

[14] Legge M. Amniotic fluid pre-albumin and retinol binding protein in complicated pregnancies. *Aust NZ J Obstet Gynaecol* 1983; **23**:77–8.

[15] Guignard JP, Torrado A, Da Cunha O, Gautier E. Glomerular filtration rate in the first three weeks of life. *J Pediatr* 1975;**87**:268–72.

[16] Siegel SR, Oh W. Renal function as a marker of human fetal maturation. *Acta Paediatr Scand* 1976;**65**:481–5.

[17] Rudd PT, Hughes EA, Placzek MM, Hodes DT. Reference ranges for plasma creatinine during the first month of life. *Arch Dis Child* 1983;**58**:212–5.

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Why nebulise for more than five minutes?

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SUMMARY The output of the drug and the particle size produced by various nebulisers were assessed, and sensible nebulisation times for sodium cromoglycate calculated. Three of the four nebuliser systems tested produced over 80% of total drug output within the first five minutes of nebulisation. We suggest that five minutes is an optimum nebulisation time for sodium cromoglycate using these nebuliser combinations.

Nebulisation treatment can upset both child and parent, especially when it is prolonged. Parents frequently report spending up to 20 minutes nebulising a 2 ml charge of sodium cromoglycate. As evaporation makes it impossible to determine output of the drug directly from weight loss of the nebuliser chamber, we have used a multistage liquid impinger to determine output of the drug and aerosol particle size. This has enabled us to suggest an optimum nebulisation time for sodium cromoglycate using the nebuliser combinations available in our department.

Methods

A multistage liquid impinger as described by May,[1] and later modified by Bell,[2] was used to assess the aerodynamic particle size distribution of the aerosol clouds. The device consist of a 'throat' that contains a right angle bend (to simulate the oropharynx) and four impaction stages. Stages 1, 2, and 3 consists of impaction jets together with sintered glass collecting discs. Water is placed in each stage to keep the upper surfaces of the collection discs moist. The fourth stage consists of a narrow jet aimed at the base of the collection chamber.

The impinger had been calibrated by sampling an aerosol of dibutyl phthalate droplets that had been sized by a reference impactor (Cassella impactor). A 50% cut off diameter was derived for each stage of the device and was expressed in terms of aerodynamic diameter. The aerodynamic diameter of a droplet is the diameter of a unit density spherical particle with the same settling velocity as the droplet in question.

The impinger was assembled as shown (figure) and a vacuum pump used to establish a flow rate of 60 l/minute through the device. The flow rate was adjusted by a pressure relief valve and was measured with a gas flow meter. Two ml of a 1% sodium cromoglycate solution was put into the reservoir of the nebuliser chamber with a pipette. The nebuliser chamber was fixed so that the mouthpiece was central and about 2 mm from the 'throat' of the impinger before nebulisation.

The drug output characteristics from four of each of the following nebulisers run for periods of 5, 10, and 15 minutes were determined: Pari Inhalierboy; Novair compressor with Cirrhus nebuliser chamber (Intersurgical Ltd); Medix Traveller (System B) (Medix Ltd); and the Nebupump compressor (Corri-Med Ltd) with Unicorn nebuliser chamber (Medic Aid Ltd).

After nebulisation, the various stages of the impinger were washed out quantitatively using distilled water into 100 ml volumetric flasks. The amount of anhydrous sodium cromoglycate was assayed spectrophotometrically using a wavelength of 356 nm. The spectrophotometer had previously been calibrated using solutions of known concentrations of sodium cromoglycate. The absorbance for a 1% solution using a 1 cm silica curvette was measured as 166. The weight loss during nebulisation was calculated by weighing before and after nebulisation. The volumetric flow rate of air through the nebuliser was measured in a separate experiment by connecting a rotameter upstream of the nebuliser after sealing the nebuliser to prevent leaks.

Average nebulisation rate (N) was calculated as: $N=M/Co\times t$, where M=mass of sodium cromoglycate in the nebulised cloud, Co=initial concentra-

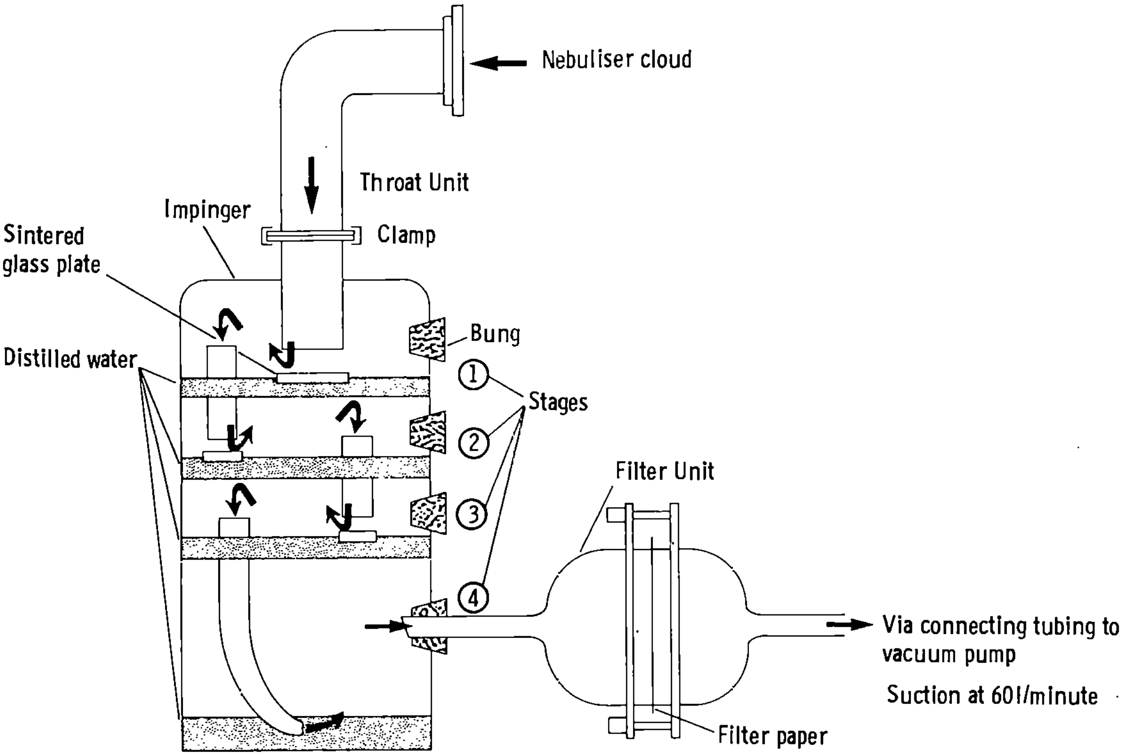

Figure *Diagram of multistage liquid impinger. The aerosol cloud is sucked through the device at 60 l/minute. Larger particles impact on the upper stages, smaller ones on the lower stages. The solution can then be assayed in individual stages to determine the amount of drug present in specific particle size ranges.*

tion of sodium cromoglycate in reservoir solution, and t=time (minutes).

The average evaporation rate was calculated by subtracting the nebulisation rate from the rate of weight loss.

Using the data acquired from the Multistage impinger together with the 50% cut off diameters for each stage of the device, a plot of aerodynamic size against cumulative percentage undersize was constructed. From this graph the following measurements were calculated: mass median aerodynamic diameter, which is the diameter of droplets such that half of the aerosol mass is contained in smaller droplets and half in larger droplets, and the geometric standard deviation, which is the ratio of 84·1% diameter to the 50% (mass median aerodynamic diameter) diameter; the value of the geometric standard deviation is a measure of width of the droplet distribution. The percentage of the aerosol mass contained in droplets of less than 4·4 μm was also calculated.

Results

The mean airflow rate downstream of the nebuliser, average nebulisation rate, and average rate of weight loss caused by evaporation are shown in table 1. Between 20% (Novair compressor with Cirrhus nebuliser chamber) and 50% (Medix traveller with Chamber B) of the total weight loss during nebulisation is caused by evaporation.

The drug output after various times of nebulisation, the mass median aerodynamic diameter, and the geometric standard deviation of the four types of nebuliser are shown in table 2. When using the Pari Inhalierboy, Novair compressor and Cirrhus nebuliser chamber, and Medix traveller and Chamber B, over 80% of the drug was delivered in the first five minutes of nebulisation. The Nebupump compressor in combination with the Unicorn chamber had a much slower output—less than 50% at five minutes.

Although the Pari Inhalierboy had the greatest

Table 1 *Air flow rate, nebulisation rate, and rate of weight loss caused by evaporation for four commonly used nebulisers: four of each type were tested. Results were obtained using a fill volume of 2 ml of a 1% sodium cromoglycate solution. Figures are given as mean (SD)*

	Mean air flow rate downstream of nebuliser (l/min)	*Average nebulisation rate (ml/min)*	*Average rate of weight loss caused by evaporation (ml/min)*
Pari Inhalierboy	4·1 (0·3)	0·18 (0·02)	0·09 (0·003)
Novair Compressor with Cirrhus nebuliser chamber	5 (0·5)	0·14 (0·2)	0·04 (0·008)
Medix Traveller with Chamber B	6 (0·3)	0·08 (0·002)	0·08 (0·008)
Nebupump Compressor with Unicorn nebuliser chamber	3·2 (0·3)	0·063 (0·005)	0·04 (0·003)

Table 2 *Drug output, mass median aerodynamic diameter, and geometric standard deviation for four commonly used nebulisers: four of each type were tested. Figures are given as mean (SD)*

	Total output of sodium cromoglycate (mg)			*Percentage of drug contained in particles <4·4 μm*	*Mass median aerodynamic diameter (μm)*	*Geometric standard deviation*
	At 5 min	*At 10 min*	*At 15 min*			
Pari Inhalierboy	9·2 (0·32)	9·35 (0·54)	9·38 (0·5)	40	6·1	2·13
Novair Compressor with Cirrhus nebuliser chamber	7·1 (0·47)	8·4 (0·61)	8·8 (0·6)	84·5	2·0	2·2
Medix Traveller with Chamber B	7·5 (0·45)	8·15 (0·49)	8·25 (0·5)	79·8	2·3	2·34
Nebupump compressor with Unicorn nebuliser chamber	3·13 (0·4)	6·1 (0·42)	7·9 (0·45)	82·6	2·6	3·07

output at five minutes its mass median aerodynamic diameter was 6·1 μm, compared with one of 2–2·6 μm for the other combinations.

Discussion

We have shown that in three of our nebulisers—the Pari Inhalierboy, Novair, and Medix Traveller, over 84% of the total drug delivery from a unit dose charge occurs within the first five minutes. We now advice nebulisation for five minutes only, thus improving compliance. The Nebupump, however, with a slow delivery rate, delivered 3·13 mg of sodium cromoglycate during the first five minutes, and doubled this over the next five minutes, to deliver a total of 6·05 mg during the 10 minute period. This prolonged duration of delivery makes it less attractive for paediatric use. The Nebupump compressor produces low flow rate through the nebuliser chamber compared with the other compressor, which is the reason for the slow output. In separate studies the Unicorn chamber performed as well as the Cirrhus chamber and Chamber B when driven by a similar compressor (unpublished observations).

It is important to explain to parents that effective nebulisation finishes while there are still droplets visible in the nebuliser chamber. Parents are often found struggling to hold the facemask to their child's face for up to 30 minutes until these droplets finally evaporate.

Droplets of more than 8 μm tend to be captured in the oropharnyx of adults,[3] while droplets of less than 5 μm are considered ideal for penetration into the lungs.[4] In young children the airways are smaller and it is possible that the optimal droplet diameter is even less, especially in infancy when nose breathing may predominate.

It was interesting that the mass median aerodynamic diameter was similar for all of the nebulisers, except the Pari Inhalierboy, which produced an aerosol with a much larger diameter. Thus although the Pari Inhalierboy produces the most drug at five minutes, many of the particles produced may well be too large to enter the respiratory tract, especially in a young child. In theory therefore it may deliver less drug to the lungs than the Novair and Medix nebulisers.

Using a Multistage liquid impinger it is possible to separate aerosol droplets into various fractions depending on their aerodynamic size. The quantity of sodium cromoglycate in each fraction can be determined using a spectrophotometric assay. Each test took under two hours to do.

This well established method offers a way of defining the drug output and particle size distribution of commonly used nebulisers and aerosols, which may provide useful information when interpreting trials of nebulised drugs. It is also possible to work out the amount of drug in particles less than a particular size range—for example, the amount of drug in particles less than 1 µm, or less than 2 µm, and so on; various nebulisers and nebuliser solutions could easily be assessed using this system. This may help to suggest sensible nebulisation times for the equipment and drug used. Newman *et al* have shown that by increasing the volume fill by adding more diluent, a greater proportion of the original dose may be released.[5] This would considerably increase the nebulisation time. In this study we have only considered the recommended dose.

It is clear from the results that an appreciable amount of weight loss from the nebuliser is from evaporation. Thus weight loss cannot be used as a method of measuring drug output.

References

[1] May KR. Multi-stage liquid impinger. *Bacteriological Reviews* 1966;**30**:559–70.

[2] Bell JH, Brown K, Glasby J. Variation in delivery of isoprenaline from various pressurised inhalers. *J Pharm Pharmacol* 1973;**25**:(suppl) 32–6.

[3] Swift DL. Aerosols and humidity therapy. *Am Rev Respir Dis* 1980;**122**:71–7.

[4] Clay MG, Pavia D, Clarke SW. Effect of aerosol particle size on bronchodilation with nebulised terbutaline in asthmatic subjects. *Thorax* 1986;**41**:364–8.

[5] Newman SP, Pellow PGD, Clay MM, Clarke WC. Evaluation of jet nebulisers for use with gentamicin solution. *Thorax* 1985;**40**:671–6.

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Tumour necrosis factor-α in infectious meningitis

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SUMMARY During a one year period tumour necrosis factor-α (TNF-α) was prospectively determined in the cerebrospinal fluid of 49 patients with infectious meningitis. TNF-α was found in the cerebrospinal fluid of 15 of 18 patients with bacterial meningitis. In 11 patients who had cerebrospinal fluid positive for TNF-α it was detected in only one serum (in low concentration). There was no significant correlation between the concentration of TNF-α in cerebrospinal fluid and the patient's age, duration of illness and fever, body temperature, and serum C reactive protein. However, cerebrospinal fluid protein concentrations of ≥2 g/l and leucocyte values of $\geq 2 \cdot 5 \times 10^9$/l were more often associated with high TNF-α concentrations (≥500 pg/ml). In contrast with bacterial meningitis, none of the 31 samples of cerebrospinal fluid from patients with viral meningitis was positive for TNF-α. Thus this investigation supports the conclusion, drawn from animal studies on TNF-α in the cerebrospinal fluid, that the presence of TNF-α is indicative of bacterial meningitis. Absence of TNF-α cerebrospinal fluid, however, was found here not to exclude a bacterial aetiology of the infection.

Tumour necrosis factor-α (TNF-α) was defined originally as a substance that is found in serum of animals sensitised to the *Mycobacterium bovis* strain BCG or *Corynebacterium parvum,* challenged later with endotoxin, and that causes the necrosis of some tumours when passively transferred to tumour bearing animals.[1] TNF-α is a macrophage derived cytokine that not only has antitumour activity but also functions as a central mediator of the inflammatory response. It has been shown to be a critical factor involved in the onset of septic shock.[2] In addition, TNF-α is identical to cachectin, which suppresses the activity of lipoprotein lipase and thus causes hypertriglyceridaemia and cachexia; both are associated with chronic infections.[1]

New information about the role of TNF-α in infections of the central nervous system has emerged recently from animal studies. TNF-α was detected in the cerebrospinal fluid but not in serum of mice infected with *Listeria monocytogenes.*[3] However, acute lymphocytic choriomeningitis virus induced meningitis was not paralleled by production of TNF-α in the central nervous system. In these studies TNF-α was also identified in three of seven patients with bacterial meningitis but in none of seven patients with aseptic meningitis.[3] To substantiate these preliminary findings we prospectively determined TNF-α in the cerebrospinal fluid of children with infectious meningitis. Additionally, available sera from children with bacterial meningitis drawn in parallel with cerebrospinal fluid were retrospectively analysed for TNF-α. The findings were correlated with clinical, microbiological, and routine laboratory data.

Patients and methods

PATIENTS

In the University Children's Hospital of Zurich 205 children with suspected meningitis were seen from 1 October 1987 to 30 September 1988 from a total of 5000 inpatients and 19 400 outpatients. Clinical and laboratory data confirmed the diagnosis of meningitis in 56 patients. History and clinical data were gathered by chart review, and special attention was paid to duration of symptoms and antibiotic treatment in the days before admission. Seven of the 56 patients with meningitis were not investigated for TNF-α as they were admitted to intensive care; two of these patients died. Therefore 49 patients were included in the study.

METHODS

Cerebrospinal fluid was obtained by atraumatic lumbar puncture for direct inoculation of bacterial culture media (chocolate agar and thioglycolate with saccharose). Additional cerebrospinal fluid was collected in three sterile tubes. One tube with approximately 1 ml of cerebrospinal fluid was centrifuged immediately at 3000 rpm for 15 minutes. Half the volume of the supernatant was coded and frozen at −20°C until used for determination of TNF-α, the other half volume was used for detection of bacterial antigen using a commercially available latex slide agglutination test (Becton Dickinson). The pellet served for preparation of Gram stained slides. Within one hour after the samples were obtained, the second and the third tube were processed in the clinical laboratory for determination of the number of leucocytes and leucocyte differential count, and for glucose and protein concentrations. These determinations were done by standard methods.

Blood was drawn for bacterial cultures (at least in all patients with turbid cerebrospinal fluid), differential cell count, platelets, and determination of serum C reactive protein and blood glucose concentrations. The specimens were processed within one hour after sampling by standard methods. Whenever available stored sera from children with both proved bacterial meningitis and TNF-α positive cerebrospinal fluid were retrospectively used for TNF-α determination.

ASSAYS FOR TNF-α

TNF-α was measured by two different methods. First, the classical bioassay with TNF-α sensitive L-M cells was used.[3] The results are given in units of TNF-α per ml (U/ml), one unit was defined as the amount resulting in lysis of 50% of the L-M cells. When testing human recombinant TNF-α the detection limit was found to be about 0·3 U/ml. For characterisation of the cytotoxic activity in cerebrospinal fluid, the samples were incubated with an excess of antirecombinant human TNF-α antiserum or with control rabbit serum. After incubation for three hours at 37°C residual cytotoxic activity was determined by adding the test samples to the L-M cells. In the second assay, TNF-α was quantitated by enzyme linked immunoadsorbent assay (ELISA) as described previously.[4] Briefly, an affinity purified rabbit antibody was used as capture antibody and a mouse monoclonal antibody labelled with horseradish peroxidase was used as the second antibody in a sandwich ELISA. The results are expressed in pg/ml and the detection limit was 32 pg/ml.

Results

PATIENTS

Forty nine children (30 boys and 19 girls) were enrolled in the study. Bacterial meningitis was found in 10 boys with a mean age of 3·5 years (range 1·3–8·8) and in eight girls with a mean age of 4·9 years (range 0·2–16·7). The diagnosis of bacterial meningitis was based on bacterial culture or bacterial antigen detection in cerebrospinal fluid. The agents grown from cerebrospinal fluid were *Haemophilus influenzae* type b (10/18), *Neisseria meningitidis* type C (3/18), *N meningitidis* type B (3/18), and *N subflava* (1/18). Furthermore, in one child who had been pretreated with antibiotics and who had sterile cerebrospinal fluid cultures *N meningitidis* type C/W135 antigen was detected in the cerebrospinal fluid. Viral meningitis was diagnosed in 20 boys with a mean age of 7·7 years (range 0·8–13·9) and in girls with a mean age 7·5 years (range 0·1–12·4). The diagnosis of viral meningitis was based on absence of bacterial growth in culture, absence of bacterial antigen in cerebrospinal fluid, and no evidence for bacteria in a Gram stain of the cerebrospinal fluid.

TNF-α IN CEREBROSPINAL FLUID

TNF-α in cerebrospinal fluid was detected in 15

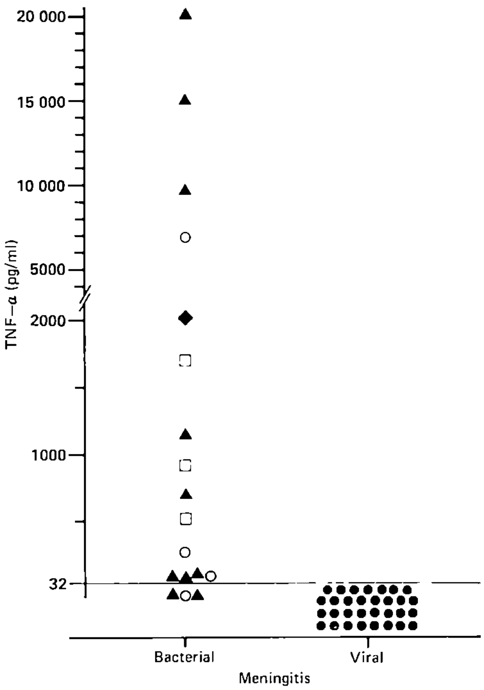

Fig 1 *Concentrations of TNF-α in cerebrospinal fluid of 18 children with bacterial and 31 children with viral meningitis.* ▲ *Haemophilus influenzae type b;* ○ *Neisseria meningitidis type C;* □ *N meningitidis type B; and* ◆ *N subflava.*

(83%) of the 18 children with bacterial meningitis; in 12 (66%) of these cerebrospinal fluid samples TNF-α was identified by both bioassay and ELISA, and in three further samples of cerebrospinal fluid only by ELISA. The concentrations of TNF-α in cerebrospinal fluid ranged from 30 to 2160 U/ml (mean 586) when measured by bioassay and from 57 to 20 235 pg/ml (mean 3991) when determined by ELISA. No TNF-α could be detected in the cerebrospinal fluid of the 31 children with viral meningitis as assessed by the ELISA technique (fig 1). There was no correlation between the concentration of TNF-α in the cerebrospinal fluid and the causative bacterium.

COMPARISON OF PATIENTS WITH AND WITHOUT TNF-α IN CEREBROSPINAL FLUID

History and clinical and laboratory data of the 49 patients studied are summarised in table 1. With respect to the recorded data patients with bacterial meningitis and TNF-α positive cerebrospinal fluid did not differ from those with TNF-α negative cerebrospinal fluid except for the mean leucocyte count (3·7 compared with 6·1×10^9/l). Compared with patients with TNF-α positive cerebrospinal fluid, the three children with bacterial meningitis and absence of TNF-α in their cerebrospinal fluid showed a longer duration of illness and fever with mean values of 48 compared with 23·3 hours and 48 compared with 22·2 hours, respectively. This, however, was due to the only child who had been pretreated with antibiotics whose illness lasted 96 hours. In both other children illness and fever had started 24 hours before admission and *H influenzae* type b was found to be the causative agent. One of these two latter children with TNF-α negative cerebrospinal fluid had the highest leucocyte count of the whole cohort studied. None of the 18 children with bacterial meningitis presented with or developed symptoms of septic shock. All showed a clinically satisfying response to parenteral treatment with ceftriaxone (60–100 mg/kg/body weight/day for seven days). There was no adverse outcome or death.

Children with viral meningitis had a longer mean duration of illness and fever, a lower mean concentration of serum C reactive protein, lower mean leucocyte count in blood and cerebrospinal fluid, and lower mean protein concentration in cerebrospinal fluid than patients with bacterial meningitis.

COMPARISON OF TNF-α CONCENTRATIONS IN CEREBROSPINAL FLUID AND SERUM

Eleven stored serum samples drawn in parallel to cerebrospinal fluid from children with detectable TNF-α in their cerebrospinal fluid were available for TNF-α determination. All these sera but one were negative for TNF-α (table 2). The amount of TNF-α in this positive serum was below 10% of the concentration in the corresponding cerebrospinal fluid. This child with detectable TNF-α in his serum had a six hour history of illness and *H influenzae* type b grew from cerebrospinal fluid and blood culture. Compared with him the other 10 children with detectable TNF-α in their cerebrospinal fluid, but no TNF-α in the serum, had a history of 12 to 48 hours (mean 26·8). In six of these 10 children blood cultures were positive (*H influenzae* type b: 2/6, *N*

Table 1 *Details of children with meningitis (n=49). Results are mean (range)*

	Bacterial meningitis				*Viral meningitis*	
	TNF-α positive (n=15)		*TNF-α negative (n=3)*		*TNF-α negative (n=31)*	
Clinical features on admission:						
Age (years)	4·4	(0·2–16·7)	3·1	(1·0–5·8)	7·6	(0·1–13·9)
Duration of illness (hours)	23·3	(3–48)	48	(24–96)	45	(4–144)
Duration of fever (hours)	22·2	(3–48)	48	(24–96)	42	(0–144)
Temperature (°C)	39·3	(38·6–40·0)	39·3	(38·6–41·0)	38·7	(37·8–40·8)
Blood:						
Serum C reactive protein (mg/l)	154	(29–369)	159	(35–98)	18	(<1–79)
Leucocyte (×10^9/l)	15·4	(2·4–33·1)	18·4	(9·3–24·9)	11·45	(4·3–22·1)
Neutrophils, band forms (%)	56	(34·5–74)	50·6	(34·5–70·5)	36·8	(9·5–61)
Neutrophils, segmented forms (%)	20	(4·5–38·5)	24·6	(11·5–33·5)	34·8	(19·5–68)
Cerebrospinal fluid:						
Leucocytes (×10^9/l)	3·7	(0·02–10·2)	6·1	(1·2–15·2)	0·2	(0·02–1·00)
Polymorphonuclear (×10^9/l)	3·4	(0·02–8·9)	5·5	(1·1–14·0)	0·1	(0·003–0·62)
Mononuclear (×10^9/l)	0·3	(0·005–1·4)	0·6	(0·1–1·2)	0·1	(0·001–0·43)
Protein (g/l)	2·3	(0·3–4·35)	1·7	(0·43–3·7)	0·49	(0·05–0·76)

TNF-α determined by ELISA.

meningitidis type B: 2/6, and *N meningitidis* type C: 2/6), whereas in the other four children *H influenzae* type b, *N meningitidis* type B or C, or *N subflava* were grown from cerebrospinal fluid only.

Table 2 *Concentrations of TNF-α (pg/ml) in cerebrospinal fluid and serum of 11 children with bacterial meningitis*

Patient No	*Cerebrospinal fluid*	*Serum*
1	20 235	<32
2	15 100	<32
3	2 070	<32
4	1690	<32
5	1465	127
6	915	<32
7	534	<32
8	253	<32
9	85	<32
10	65	<32
11	57	<32

ASSOCIATION BETWEEN TNF-α CONCENTRATIONS IN CEREBROSPINAL FLUID AND OTHER FEATURES

No clear cut correlation was found between the concentration of TNF-α in cerebrospinal fluid and age, duration of illness and fever, body temperature, leucocyte count in blood and cerebrospinal fluid, concentration of reactive protein in serum and protein in cerebrospinal fluid, respectively (table 1, fig 2). Compared with cerebrospinal fluid with low TNF-α concentrations, however, cerebrospinal fluid with protein ≥2 g/l and leucocytes ≥$2{\cdot}5\times10^9$/l were more often associated with high TNF-α concentrations of ≥500 pg/ml. This value represents 2·5% of the maximum TNF-α concentration detected in this study: high leucocyte and protein content was detected in three of nine patients with low TNF-α, and in six of nine patients with a high TNF-α concentration.

Discussion

In a recent study of mice with experimental mening-

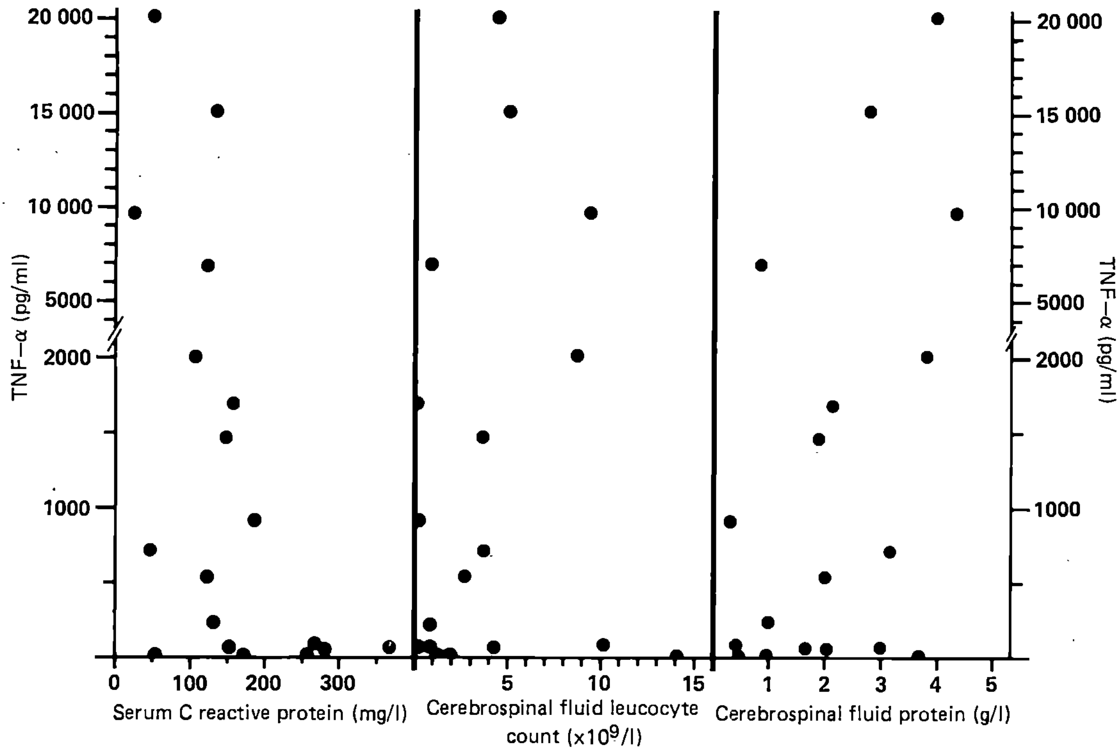

Fig 2 *Association of TNF-α in cerebrospinal fluid with serum C reactive protein, leucocyte count, and protein concentration in 18 children with bacterial meningitis.*

itis TNF-α was detected in cerebrospinal fluid early after initiation of bacterial but not at any time during virally induced disease.[3] In the present study of 49 patients with infectious meningitis TNF-α was also found only in cerebrospinal fluid of patients with bacterial (15/18) but not in subjects with viral (0/31) meningitis. As all but one sera of patients with TNF-α positive cerebrospinal fluid lacked detectable amounts of TNF-α it can be assumed that TNF-α is produced intrathecally. This hypothesis is further substantiated by recent in situ hybridisation studies showing TNF-α transcript positive cells within the inflammatory cell infiltrates in the meninges of mice with *L monocytogenes* induced meningitis (manuscript in preparation).

The lack of detectable TNF-α in the cerebrospinal fluid of three of 18 patients with bacterial meningitis might have been due to the sensitivity of the assays in use. However, in one of the three patients antibiotic pretreatment could have resulted in a reduction of micro-organisms triggering production and secretion of the cytokine. In the second child, who had the most pronounced pleocytosis, TNF-α might have been bound to or degraded by the extremely augmented cells and thus have escaped detection. For the negative results in the third patient we could not find a plausible reason. As a hypothesis, however, individual differences in the sensitivity of macrophages to respond to bacterial infections with production of TNF-α could contribute to the absence of TNF-α in the cerebrospinal fluid of the three patients with bacterial meningitis. Indeed, at least one strain of mice (C3H/HeJ) has been reported to lack TNF-α/cachectin mRNA in macrophages exposed to low amounts of endotoxin. In addition, a post-transcriptional defect prevented the production of the protein.[5]

In a recent study on Gram negative septicaemia with purpura fulminans the serum of 30 of 35 patients was positive for TNF-α, the concentrations being significantly higher in the patients who died than in the survivors.[6] Furthermore, of 79 patients with meningococcal disease TNF-α was detected in 10 of 11 patients who died but from only eight of 68 survivors of the disease.[7] Despite septicaemia with Gram negative micro-organisms in six patients, 10 of 11 serum samples tested for TNF-α in our study were negative for the cytokine investigated. None of these 10 patients suffered from septic shock, however, and all showed a clinically satisfying response to antibiotic treatment. Thus our findings would be compatible with the suggestion that the presence of high concentrations of TNF-α in serum could be indicative of severe disease. In fact in animal studies intravenous injection of TNF-α/cachectin into rats causes haemorrhagic necrosis, which is indistinguishable from the pathologic effects seen after endotoxin administration.[8]

Production of TNF-α within the central nervous system could be important in initiating damage of the blood brain barrier and the tissue injury observed in bacterial meningitis.[9] Thus TNF-α may exert direct cytotoxic effects and/or operate by acting on polymorphonuclear cells which respond to TNF-α with increased adherence to endothelial cells, as well as increased an oxidative burst to unopsonised zymosan particles.[10 11] In the present study no clear cut correlation was found between the concentration of TNF-α in cerebrospinal fluid and duration of illness or fever, bacterial agent, leucocyte count or protein content in cerebrospinal fluid, and leucocyte count in blood or amount of serum C reactive protein. Compared with cerebrospinal fluid with low concentration of TNF-α, however, a trend for higher protein concentration (≥2 g/l) as well as leucocyte counts (≥2·5) in cerebrospinal fluid with TNF-α concentrations ≥500 pg/ml was observed. These findings, which would be in agreement with the effects of TNF-α described on endothelial cells and granulocytes, have to be further investigated in future studies comprising larger groups of patients.

The examination of cerebrospinal fluid for TNF-α may be helpful in differentiating between bacterial and viral meningitis in patients with acute disease. Detectable TNF-α in cerebrospinal fluid was indicative for bacterial meningitis and could be used as diagnostic variable before results of culture are available, especially in cases where leucocyte count, Gram stain, or antigen detection in cerebrospinal fluid are not conclusive. The absence of TNF-α in cerebrospinal fluid, however, did not exclude a bacterial aetiology of meningitis.

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References

[1] Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. *N Engl J Med* 1987;**316**:379–85.

[2] Cerami A, Beutler B. The role of cachetin/TNF in endotoxic shock and cachexia. *Immunology Today* 1988;**9**:28–31.

[3] Leist TP, Frei K, Kam-Hansen S, Zinkernagel RM, Fontana A. Tumor necrosis factor α in cerebrospinal fluid during bacterial, but not viral meningitis. *J Exp Med* 1988;**167**:1743–8.

[4] Prince WS, Harder KJ, Saks S, Reed BR, Chen AB, Jones AJS. ELISA for quantitation of tumor necrosis factor α in serum. *Journal of Pharmacology and Biomedical Analysis* 1987;**5**: 793–802.

[5] Beutler B, Krochin N, Milsark IW, Luedke C, Cerami A. Control of cachectin (tumor necrosis factor) synthesis: mechanisms of endotoxin resistance. *Science* 1986;**232**:977–80.

[6] Girardin E, Grau GE, Dayer J-M, *et al.* Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. *N Engl J Med* 1988;**319**:397–400.

[7] Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. *Lancet* 1987;**i**:355–7.

[8] Tracey KJ, Beutler B, Lowry SF, *et al.* Shock and tissue injury induced by recombinant human cachectin. *Science* 1986;**234**: 470–4.

[9] Quagliarello VJ, Long WJ, Scheld WM. Morphologic alterations of the blood-brain barrier with experimental meningitis in rat. *J Clin Invest* 1986;**77**:1084–95.

[10] Larrick JW, Graham D, Toy K, Lin LS, Senyk G, Fendly BM. Recombinant tumor necrosis factor causes activation of human granulocytes. *Blood* 1987;**69**:640–4.

[11] Ming WJ, Bersani L, Mantovani A. Tumor necrosis factor is chemotactic for monocytes and polymorphonuclear leukocytes. *J Immunol* 1987;**138**:1469–74.

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Onset and severity of hearing loss due to congenital rubella infection

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SUMMARY Of 111 children born in 1978–82 with congenital rubella infection, confirmed by the detection of rubella specific IgM shortly after birth, 68 were reported to be hearing impaired when notified to the National Congenital Rubella Surveillance Programme (NCRSP). The average age at which the diagnosis of hearing impairment was confirmed was 11·6 months. Recent audiograms showed a hearing loss that was usually uniform across all frequencies, equal in both ears and severe, averaging 93 dB across the range 250–4000 Hz. Despite the early diagnosis of congenital rubella and the known risk of deafness, only eight of 57 infants had been tested for auditory evoked responses in the first 6 months of life; all eight had severe hearing loss. Evidence of progressive hearing loss was found in only one of the 57 children. Definitive hearing tests (as distinct from screening tests) were frequently delayed until after the first birthday. Newborn babies identified as being at high risk of congenital deafness should have a full audiological assessment in early infancy.

Rubella infection acquired during early pregnancy may cause congenital defects, of which sensorineural deafness is by far the most common and often occurs in isolation.[1] Although the hearing loss is usually identified in early childhood, there have been reports of children with a progressive auditory impairment beginning several years after birth.[2] The diagnosis of congenital rubella in some studies was based on clinical grounds alone,[3] however, and in others on the presence of IgG antibodies to rubella that could have been acquired postnatally.[4] It is therefore possible that in some cases deafness was not caused by intrauterine rubella infection but was due to some other cause, for example, autosomal recessive inheritance.[5]

Laboratory tests for rubella specific IgM allow a more accurate diagnosis of congenital rubella infection to be made in newborn babies who have been exposed to the virus in utero.[6] If the infection occurs before the 18th week of pregnancy there is a high risk of sensorineural hearing loss,[1] even if the child appears unaffected at birth. A conductive loss may be superimposed in later childhood.[1]

Early detection and treatment of severe hearing impairment has been shown to result in a much better long term functional outcome.[7] Knowledge of the onset, severity, and progression of hearing loss in children with confirmed congenital rubella infection would indicate the appropriate timing of hearing tests and duration of follow up. A retrospective review of the progress of deafness in a large cohort of children with congenital rubella that had been proved in the laboratory was therefore undertaken. In addition to providing information about the natural history of this disorder, the effectiveness of the services involved in the detection of hearing loss in early childhood has been assessed.

Methods

The records of the National Congenital Rubella Surveillance Programme (NCRSP) were examined and 117 children born in the five years 1978 to 1982 in whom congenital rubella was diagnosed by the detection of rubella specific IgM in early infancy were identified. The physician who notified each child was contacted and asked to provide further information. For children known to have a hearing loss, this included the age at which it was first suspected, by whom, and the age at which it was confirmed. For those children believed to have normal hearing or for whom this information was not available at the time of notification we attempted to determine the normality or otherwise of hearing.

The timing and results of past hearing tests were obtained for children with a hearing loss, and wherever possible a recent pure tone audiogram was obtained for all children in the study.

Results

Of the 117 children identified, five had died and one had emigrated; these children were excluded from further analysis. Of the remaining 111 children, 68 (61%) were recorded as having a hearing loss, 37 were initially reported to have normal hearing, and six had not had accurate testing because of developmental delay (table).

Replies to the request for details of the age at which a hearing loss was first suspected, and then confirmed, were obtained for 57 of the 68 children reported to have a hearing loss. The mean age at which the hearing loss was suspected and confirmed were 7·9 months and 11·6 months respectively. Parents were usually the first to suspect a hearing deficit (22 cases), but paediatricians (14 cases), health visitors (seven cases), audiology and ear, nose, and throat clinics (four cases), and clinical medical officers (three cases) also identified previously unsuspected cases.

In the first six months of life only eight of these children were tested for auditory evoked responses and in each case these were abnormal. Unfortunately it was not possible to determine retrospectively whether these children were tested because of their high risk of deafness or because of clinical suspicion of a hearing loss. In the second six months, 24 children had their hearing loss diagnosed by distraction tests. Six children had been reported as having normal hearing when tested by this method, however, and it is likely that a number of those whose hearing loss was detected after the first year also 'passed' a distraction screening test in infancy.

A significant hearing loss had been confirmed by the end of the first year in 37 cases, and by the age of 18 months in a further 13 children. None of these children showed any evidence of deterioration in hearing after the diagnosis had been established. Of the remaining seven children, six were identified as hearing impaired between 22 and 42 months (the age was unknown in one case). One of these children had a clearly documented deterioration over a five year period after initially appearing to have normal hearing. The reasons for delay in diagnosis in the other five were: failure to do appropriate tests (n=3, in two cases because the child had passed a distraction test), failure to attend follow up appointments (n=1), and difficulty in evaluating a moderate mixed hearing loss (n=1). There was no evidence of a progressive hearing loss in any of these children.

A recent pure tone audiogram was obtained for 50 of the 68 children with a known hearing loss at a mean age of 6·9 years (range 3·5 to 8·5). The best point for the better ear on these audiograms was between 40–60 dB for 13 children, 61–80 dB for 13 children, and 81–100 dB for 17 children. A further five children had no hearing below 101 dB and only two had hearing at better than 40 dB loss. The mean best point for the better ear was 76·0 dB for the whole group.

There did not appear to be a characteristic pattern of hearing loss such as high tone deafness, but the loss was remarkably symmetrical in many cases, the maximum difference between the two ears averaging only 22 dB. The hearing deficit was usually severe with an average loss over the range 250–4000 Hz of 95 dB in the left ear and 92 dB in the right ear (figure). Pure tone audiograms were not obtained for 18 children of whom four had severe mental handicap and hearing loss, four had unmeasurable hearing levels, and 10 were not available for testing.

Of the 43 children initially reported to the NCRSP as having normal hearing or in whom testing had not been carried out, 15 subsequently had normal pure tone audiograms and a further four were reported to have normal hearing. Maternal rubella infection occurred at 20 weeks' gestation or later in four of the 15 cases with normal audiograms. Three children had a unilateral hearing loss which was mild in one case and moderate in the other two (one uniform loss, one high tone). Bilateral hearing loss was found in 10 children in this group and was severe in all but one. Of the children with a severe loss one had had abnormal responses to distraction testing at 11 months and a severe hearing loss had been

Table *Audiological follow up of confirmed cases of congenital rubella (n=117)**

Initially reported deaf (n=68)	
Audiogram not obtained	9
Severe mental retardation	5
Hearing loss—best point for the better ear (dB):	
<40	2
40–60	13
61–80	13
81–100	17
>100	9
Initially reported normal, or not tested (n=43)	
Audiogram not obtained	11
Normal hearing	19
Unilateral loss	3
Bilateral loss	10

*Five children died and one emigrated.

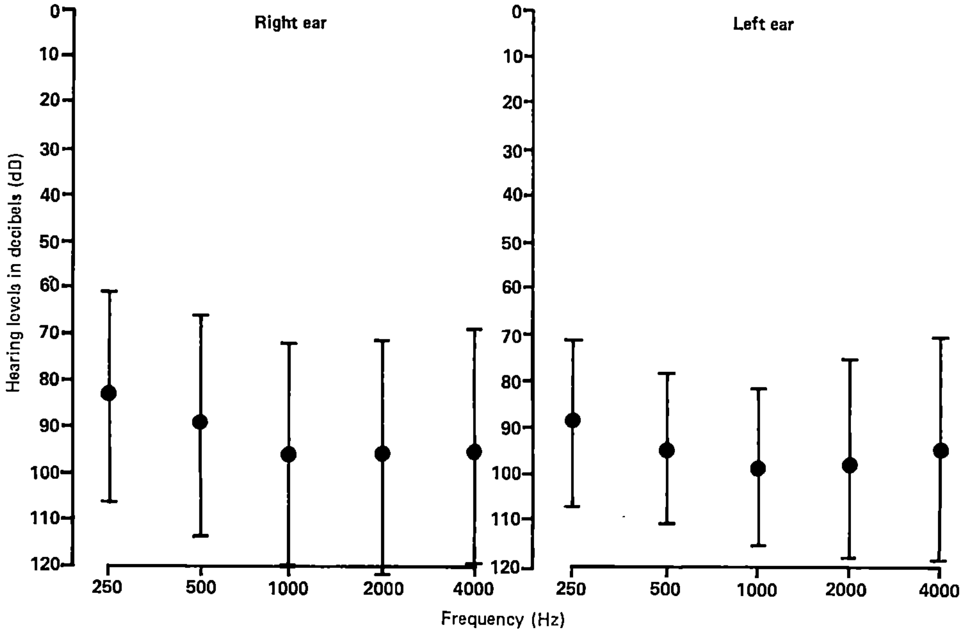

Figure *Mean (SD) hearing threshold in 50 children initially reported as hearing impaired.*

confirmed at 18 months. The deficit was identified by 2·5 and 3 years respectively in two others, but information relating to the onset was not available for the remaining six children with a severe loss. There was no evidence to suggest a later onset or progression in any of the deaf children who had initially been reported to have normal hearing. No information was available for 11 of the 43 children in this group.

Discussion

The data we have obtained confirm that the hearing loss that results from congenital rubella infection is severe and affects most children born to mothers who contract this infection before 18 weeks' gestation. However, the nature of the hearing loss we found is at variance with previously reported characteristics in two important respects. The first difference we found was that the hearing loss was surprisingly uniform across all frequencies and not a high tone deafness as is often stated.[3] Secondly, we found little evidence to support the suggestion that the hearing loss due to congenital rubella infection is progressive. Only one patient out of a total of 61 with a bilateral loss of over 40 dB had a clearly documented deterioration. By contrast, all of the eight children who had auditory evoked responses in the first six months of life were found to have severe losses. As most of the children were not tested in early life, however, we cannot be certain that the hearing loss caused by congenital rubella infection is not progressive in some infants at least in the first year of life.

Almost a third of the children in this study were not diagnosed as hearing impaired until the second or third year of life. This appeared to be the result of a combination of factors that led to either a failure to investigate, or inadequate investigation of, these extremely high risk patients. The factors included: (i) a lack of awareness of, or access to, equipment to measure brain stem evoked responses, (ii) failure of physicians to appreciate the need to assess the hearing of these children in early infancy, and (iii) reluctance of some parents to accept both the possibility of a hearing disorder and the need for testing.

In summary, the hearing loss caused by congenital rubella is usually severe and affects all frequencies uniformly. Parents of newborns at risk require careful counselling, and early audiological assessment should be arranged in a specialist centre in order to allow early amplification to be provided where appropriate.

We thank the physicians who kindly provided the information and Mrs Eileen Wood for preparing the manuscript.

References

[1] Munro ND, Sheppard S, Smithells RW, Holzel H, Jones G. Temporal relations between maternal rubella and congenital defects. *Lancet* 1987;**ii**:201–4.

[2] Anvar B, Mencher GT, Keet SJ. Hearing loss and congenital rubella in Atlantic Canada. *Ear Hear* 1984;**5**:340–5.

[3] Sheridan MD. Final report of a prospective study of children whose mothers had rubella in early pregnancy. *Br Med J* 1964;**ii**:536–9.

[4] Peckham CS. Clinical and laboratory study of children exposed in utero to maternal rubella. *Arch Dis Child* 1972;**47**:571–7.

[5] Harper PS. *Practical genetic counselling.* Bristol: Wright, 1984.

[6] Cradock-Watson JE, Ridehalgh MKS. Specific immunoglobulins in children with the congenital rubella syndrome. *J Hyg (Camb)* 1976;**76**:109–23.

[7] Markides A. Age at fitting of hearing aids and speech intelligibility. *Br J Audiol* 1986;**20**:165–7.

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Lung function in children of low birth weight

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SUMMARY Lung function was recorded in a cohort of 130 age specific children of low birth weight (under 2000 g) and a reference population of 120 unselected local schoolchildren at 7 years of age. Children of the cohort were similar in height and forced vital capacity to the reference group, but had significantly reduced forced expiratory volume in 0·75 second and expiratory flow indices. Although neonatal respiratory illness was associated with reduced airway function, we were unable to confirm that this was a consequence of oxygen treatment or mechanical ventilation. Low birth weight, however, was closely associated with poor airway function independent of neonatal respiratory illness. Other factors of importance included the male gender and maternal smoking. The reduction in airway function observed in the low birthweight children was associated with cough but not wheeze. The disparity between the relatively well preserved vital capacity and reduced airway function suggests that very low birth weight, and hence prematurity, has its greatest effect on the subsequent growth of airway function. The absence of an association between neonatal oxygen score or mechanical ventilation and childhood lung function suggests that the long term effect of neonatal respiratory treatment is small compared with that of birth weight, maternal smoking, and male sex.

Preterm infants with neonatal respiratory disorders sometimes sustain severe lung injury during mechanical ventilation.[1] The resulting clinical syndrome is called bronchopulmonary dysplasia. While it is well established that children who survive bronchopulmonary dysplasia have poor airway function at school age,[2–4] the long term lung function of most preterm infants who do not develop bronchopulmonary dysplasia has not been settled. Most early studies reported that these children recovered completely and had normal lung function at school age,[5–9] although some noted subtle abnormalities when more sensitive tests of airway function were used.[10 11] Recent studies have shown increasing evidence of reduced airway function in these children.[12–16] This disparity may in part be explained by the progressive increase in the survival of very small babies in recent years and in part by the heterogeneity of the study and control subjects in these studies.

Some authors have reported poorer lung function in small groups of children who were born prematurely and who received neonatal respiratory treatment.[14 15] Defects in study design mean that it is unclear whether their findings were attributable to treatment in the neonatal period or merely to prematurity, as control groups of children of preterm birth who did not require neonatal intensive care were not examined. Some studies had no control groups at all,[5 9 12 14 16] whereas others recruited only 'normal' controls rather than a truly representative reference population. In these studies, it is possible that a small difference in airway function between patients and the 'normal' controls was simply a result of selection bias.

Most studies are retrospective. There has been only one large cohort study.[9] The 153 subjects were recruited over a decade (1961–70) during which techniques of neonatal intensive care changed so much that the subjects were in effect derived from varied neonatal backgrounds.

In order to determine the long term effects of neonatal respiratory treatment on lung function, it is essential to study a large age specific and birthweight specific cohort of preterm children, recruited over a confined time period. The study group should be compared with a reference population of healthy (as opposed to normal) children of equivalent age.

We recently carried out a prospective study of a cohort of low birthweight children at 7 years in order to relate their lung function to birth weight, perinatal factors, and the level of neonatal intensive care which they received. We also wished to examine the clinical significance of our findings by relating lung function to current symptoms.

Subjects and methods

SUBJECTS

The cohort of low birthweight children and the reference population have previously been described.[17] Of the 189 survivors of the low birthweight cohort 134 children (71%) were available and attended our lung function clinics at 7 years (SD 0·2 years). Because of incoordination (n=2), colds (n=1), and tracheostomy (n=1), only 130 completed the tests. All weighed under 2000 g at birth, were born between June 1979 and May 1980, and were recruited at birth or on admission to our neonatal units. Perinatal events were recorded at the time the children were discharged home. A reference population of 123 unselected local schoolchildren of equivalent age (7·0 (0·4) years), none of whom weighed under 2000 g at birth, were recruited from three schools. Their selection was based on their date of birth irrespective of their previous health or family background.

All the children had lung function tests using an identical protocol and equipment. The standing height of each child was measured without shoes using either a portable or a wall mounted stadiometer (Holtain). A respiratory history was recorded on self administered questionnaires by parents.[18]

The studies were all approved by local ethics committees. Informed consent was obtained from the parents of both the low birthweight cohort and the local schoolchildren.

EQUIPMENT AND PROTOCOL

Forced vital capacity (FVC) manoeuvres were recorded using a heated pneumotachograph (Fleish No 4) and a microcomputer (Sinclair ZX 48kB). The pressure drop across the pneumotachograph was measured with a differential pressure transducer (Validyne DP45) connected to a carrier demodulator (Validyne). The flow signals were sampled on line with eight bit resolution at at least 70 Hz by the analog to digital converter and were digitally integrated to produce volume data. The device was linear up to a flow of 9 l/second, encompassing the range of flows encountered during an FVC manoeuvre. Two types of calibration were made. Firstly, the system together with a pocket spirometer (Micro-Medic Ltd), whose measurements were corrected to body temperature, pressure, and saturation, were calibrated with a five litre calibrating syringe at monthly intervals. Because of its low resistance to airflow, the effect of adding the electronic pocket spirometer on the dynamic response of the pneumotachograph was negligible. The two were never found to differ by more than 3%. Secondly, the stability of the system throughout the recording session was checked by recording each blow simultaneously with the pocket spirometer in series with the pneumotachograph. The computer was recalibrated if the readings of the computer and the pocket spirometer differed by more than 2%. At the start of an FVC manoeuvre, data storage commenced when the airflow had exceeded 140 ml/second. Recording ceased as soon as the instantaneous flow fell to zero. The flow-volume curves were displayed graphically on the visual display unit (VDU). Raw data was stored on Microdrive discs (Sinclair) for further analysis.

Before recordings commenced, each child was coached on the technique of the FVC manoeuvre. The subject was seated. A minimum of five FVC manoeuvres were made. Recordings were repeated until at least three technically satisfactory curves were obtained with the FVC within 10% of the largest value (within 5% in most cases). Where more than three curves were available, the three with the largest FVC were saved for subsequent analysis. Before calculation of lung function indices the stored flow-volume curves were visually examined for inconsistency by superimposition on the VDU screen. Curves that were affected by technical errors such as noise, hesitancy, and cough were eliminated. The following indices were calculated: FVC, forced expired volume in 0·75 seconds ($FEV_{0·75}$), mean transit time, and maximum expiratory flow at 75, 50, and 25% of FVC remaining in the lungs (MEF_{75}, MEF_{50}, and MEF_{25}). $FEV_{0.75}$ was used here because many children in the reference group had a forced expiratory time of less than one second. The indices that were obtained from the 'best' curve were used in the analysis. The 'best' curve was defined as the one with the shortest mean transit time, in accordance to recommendations of Chinn and Cotes,[19] provided that the FVC was within 2% of that of the largest recorded. In 86% of cases the 'best' curves were also the ones with the largest sum of FVC and $FEV_{0.75}$.

DATA ANALYSIS

Reference values for lung function: regression equations

There was a wide range of height among children of both groups (low birth weight 98·8–132·7 cm, control 104·0–136·0 cm). There was also a significant proportion of children of non-white origin, predominantly Asian (Indian subcontinent) and

Afro-Caribbean (low birthweight 22%, reference 44%). In order to facilitate comparison of lung function in the two groups of children, lung function indices were standardised for differences in height, sex and ethnic background, according to guidelines laid down by Cole[20] and Quanjer.[21] Linear, logarithmic, and quadratic models were examined and compared using generalised linear interactive modelling (GLIM).[22] Only predictors and interaction terms of significance ($p<0\cdot05$) were retained in the final multiple regression models. Where more than one regression model was found to explain a similar proportion of variance, the simplest one was chosen. The normality and the homosecedasity of the residuals were checked by plotting the residuals against predicted values.

The low birthweight subgroups

An oxygen score, whose definition has already been detailed,[18] together with the duration of mechanical ventilation and the peak inspiratory pressure were used as parameters of the level of neonatal respiratory treatment. Lung function was evaluated in the four clinical subgroups, as defined by the level of neonatal respiratory treatment.[18] Unpaired Student's *t* tests were used in examining differences between groups. The association between putative risk factors and childhood lung function was evaluated using correlation, one way variance, and multiple regression analysis.

Results

REFERENCE VALUES FOR LUNG FUNCTION

Satisfactory lung function recordings were obtained from 120 children of the reference group. Because of the narrow age range, age was not a significant predictor of lung function after adjusting for differences in height. Height, sex, and ethnic background were predictors for FVC, $FEV_{0\cdot75}$, and MEF_{75}. For MEF_{50} and MEF_{25}, height and Afro-Caribbean (black) group were significant predictors, whereas for peak expiratory flow rate, sex and height were the only significant predictors. As there was no significant difference in the regression coefficient for covariate height between male and female, and between white and non-white groups, the effects due to differences in sex and ethnic background were best summarised in a single equation for each lung function index as a function of height (table 1). Logarithmic models explained the same proportion of variance as linear models,

Table 1 *Standardisation equations for lung function indices derived from the reference population (n=120)*

		Residual standard deviation	*r^2*
$\log_n$ FVC =	$-11\cdot08-0\cdot09$ 'girl' $-0\cdot16$ 'black' $-0\cdot08$ 'Asian' $+ 2\cdot40 \log_n$ height	0·13	0·56
$\log_n FEV_{0\cdot75}$ =	$-9\cdot41-0\cdot07$ 'girl' $-0\cdot14$ 'black' $-0\cdot09$ 'Asian' $+ 2\cdot03 \log_n$ height	0·12	0·53
$\log_n$ PEFR =	$-5\cdot97-0\cdot09$ 'girl' $+ 1\cdot50 \log_n$ height	0·16	0·26
$\log_n MEF_{75}$ =	$-5\cdot11-0\cdot07$ 'girl' $-0\cdot10$ 'Asian' $+ 1\cdot31 \log_n$ height	0·18	0·21
$\log_n MEF_{50}$ =	$-5\cdot02-0\cdot11$ 'black' $+ 1\cdot21 \log_n$ height	0·22	0·09
$\log_n MEF_{25}$ =	$-6\cdot66-0\cdot17$ 'black' $+ 1\cdot43 \log_n$ height	0·29	0·10
$\log_n$ MTT =	$-5\cdot50+0\cdot95 \log_n$ height	0·19	0·06

FVC=forced vital capacity; $FEV_{0\cdot75}$=forced expired volume in 0·75 seconds; PEFR=peak expiratory flow rate; MEF_{75}, MEF_{50}, and MEF_{25}=maximum expiratory flow at 75, 50, and 25% of FVC; MTT=mean transit time. Units are either l or l/second except MTT which is in seconds.

Table 2 *Perinatal data of the low birthweight cohort*

	No illness (n=68)	*Oxygen only (n=25)*	*Mechanical ventilation (n=27)*	*Oxygen dependence (n=10)*
Median (range) birth weight (g)	1700 (830–1990)	1430 (900–1980)	1340 (730–1980)	1101 (790–1370)
Median (range) gestational age (weeks)	33 (28–39)	32 (27–35)	30 (27–34)	28 (27–32)
No (%) light for dates	34 (50)	6 (24)	14 (52)	3 (30)
No (%) with transient tachypnoea of newborn	5 (7)	5 (20)	10 (4)	0
No (%) with idiopathic respiratory distress syndrome*	0	11 (44)	17 (63)	6 (60)
No (%) with recurrent apnoea or bradycardia	8 (12)	10 (40)	15 (56)	10 (100)
No (%) with mother who smoked during pregnancy	18 (27)	6 (24)	8 (31)	4 (40)

*Based on radiological diagnosis in the neonatal period.

but were chosen because the normality and homosecedasity of the residuals were significantly better than for the linear models.

Our prediction equations for lung function indices compared closely with other published data obtained using similar equipment.

PERINATAL DATA AND LUNG FUNCTION

Important perinatal data for the low birthweight children are summarised in table 2. Although a large proportion of infants were light for dates, only eight were born at term.

At 7 years the mean height for the low birthweight cohort and the reference group was on the 30th and 50th centile respectively. Compared with the reference group, the low birthweight children had an equivalent FVC but significantly lower standardised $FEV_{0·75}$ and maximum expiratory flow indices (table 3).

Low birthweight children who received neonatal respiratory treatment had poorer airway function than those who did not (p<0·01). There was, however, no difference between those who received oxygen treatment alone and those who received mechanical ventilation in addition (fig 1). Among those who received oxygen treatment (n=62) and mechanical ventilation in addition (n=37), there was no correlation between the oxygen score, duration or the peak inspiratory pressure of mechanical ventilation, and subsequent airway function.

Airway function at 7 years was strongly correlated with birth weight (p<0·0001) and to a lesser extent gestational age (p<0·05). As can be seen from fig 2, the association between birth weight and $FEV_{0·75}$

Table 3 *Mean height and lung function standardised to a height of 120 cm in the low birthweight and the reference group. Results are mean (SD)*

	Low birthweight group (n=130)	*Reference group (n=120)*
Height (cm)	119·1 (5·6)	120·4 (5·8)
FVC (l)	1·39 (0·24)	1·41 (0·21)
$FEV_{0·75}$ (l)	1·16 (0·19)†	1·25 (0·17)
PEFR (l/second)	3·01 (0·61)†	3·27 (0·52)
MEF_{75} (l/second)	2·69 (0·65)†	3·01 (0·53)
MEF_{50} (l/second)	1·85 (0·54)†	2·15 (0·49)
MEF_{25} (l/second)	1·03 (0·36)†	1·20 (0·36)
MTT (seconds)	0·44 (0·12)†	0·39 (0·07)
$FEV_{0·75}$:FVC ratio*	0·84 (0·10)†	0·89 (0·07)

FVC=forced vital capacity; $FEV_{0·75}$=forced expired volume in 0·75 seconds; PEFR=peak expiratory flow rate; MEF_{75}, MEF_{50}, and MEF_{25}=maximum expiratory flow at 75, 50, and 25% of FVC; MTT=mean transit time.

*Unstandardised.

†Significance of difference between groups by unpaired *t* test: p<0·001.

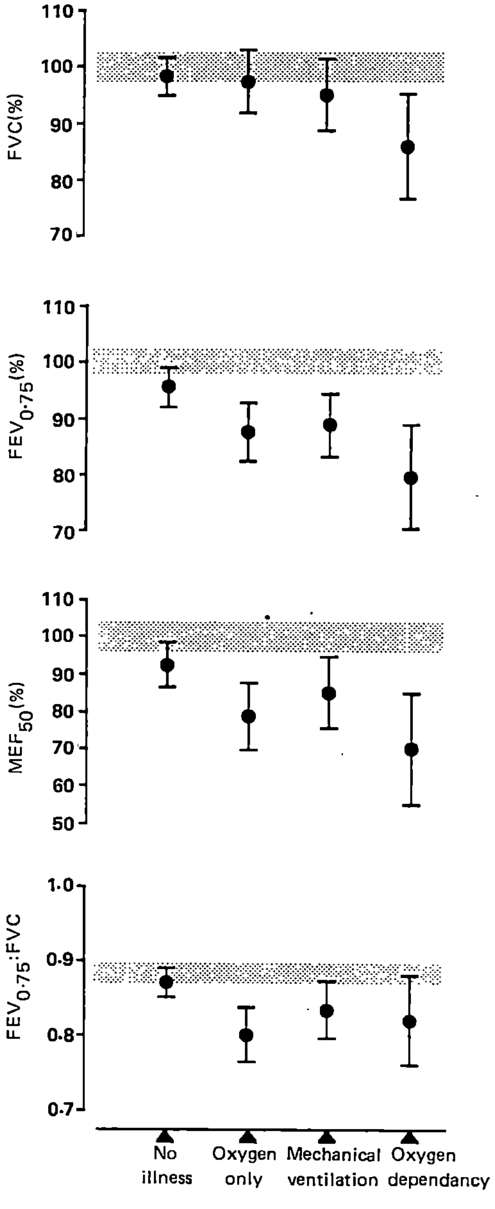

Fig 1 *Mean lung function as a percentage of the reference value (and 95% confidence interval of group mean) for low birthweight children according to clinical subgroup. Sixty eight children received no neonatal respiratory treatment, 25 children received oxygen treatment only, 27 children received mechanical ventilation in addition but did not develop oxygen dependency beyond the neonatal period, and 10 children were still oxygen dependent at 30 days of age.*
The 95% confidence interval of the mean for the reference group is indicated by shaded area.

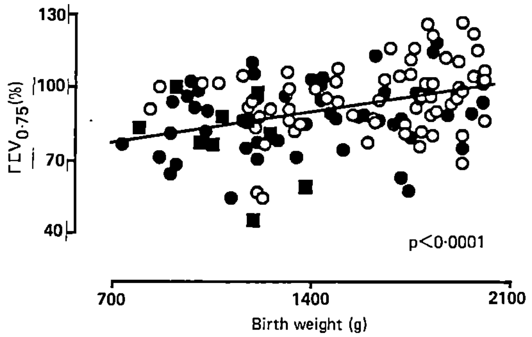

Fig 2 *Association between predicted $FEV_{0\cdot75}$ (% of reference value) at 7 years and birth weight. Open circles: no neonatal respiratory treatment (n=68); closed circles: neonatal respiratory treatment (oxygen and mechanical ventilation combined (n=52); dark squares: oxygen dependent at 30 days of life (n=10).*

was overwhelmingly more significant than that between respiratory illness and airway function. Being light for dates at birth was not associated with a poor outcome. Children who were transferred to our neonatal units after birth had poorer airway function than inborn babies. They were generally of lower birth weight and gestational age than the remainder of the cohort, and this explained the difference.

Boys had a significantly greater reduction in airway function than girls. In our reference group boys had significantly bigger FVC and $FEV_{0\cdot75}$ for height than girls. In the low birthweight cohort, although the FVC was still larger in boys, they had a marginally lower $FEV_{0\cdot75}$ than girls. Moreover, there was an excess of boys who received neonatal respiratory treatment (boys 60·9%, girls 32·8%, $\chi^2=10\cdot2$, $p<0\cdot01$) and mechanical ventilation (boys 34%, girls 18%, $\chi^2=4\cdot6$, $p<0\cdot05$). There was no difference in birth weight and gestational age between boys and girls.

Maternal smoking was also associated with reduced MEF_{75}. The mean value in relation to the predicted value was 80·7% for those whose mothers smoked and 91·4% for those whose mothers did not smoke ($p<0\cdot01$). The MEF_{50} and MEF_{25} were also significantly lower ($p<0\cdot05$), but not the $FEV_{0\cdot75}$. Children of mothers who smoked were also marginally lower in mean (SD) birth weight than the remainder of the cohort (1391 (345) g compared with 1507 (344) g, p=0·08).

As perinatal variables showed varying degrees of correlation between one another, multiple regression analysis was used to examine the association between various independent variables and airway function. It confirmed that the association between $FEV_{0\cdot75}$ and the two variables, birth weight and the male gender, was not the result of their association with neonatal respiratory illness and treatment. For MEF_{75}, maternal smoking was an additional risk factor of significance.

ASSOCIATION BETWEEN AIRWAY FUNCTION AND SYMPTOMS

Because some of the questionnaires were not completely filled, full data were available in 121 (91%) low birthweight children and 100 (83%) children in the reference group for this analysis. Using the same definition for symptoms as in the previous paper,[18] we found no association between airway function and wheeze. On the other hand, cough was associated with a reduction in airway function (table 4). A weak association between airway function and cough was also present in the reference group.

Discussion

SOURCES OF BIAS

Previous retrospective studies have the distinct disadvantage that recruitment of study subjects

Table 4 *Lung function indices expressed as percent of reference value in children with and without current symptoms at 7 years. Results are mean (SD)*

	Low birthweight group				*Reference group*			
	Wheeze		*Cough*		*Wheeze*		*Cough*	
	Yes (n=19)	*No (n=102)*	*Yes (n=41)*	*No (n=80)*	*Yes (n=16)*	*No (n=84)*	*Yes (n=17)*	*No (n=83)*
FVC	93·5 (16·4)	97·4 (14·9)	94·8 (16·7)	97·8 (14·3)	102·8 (16·9)	100·0 (11·7)	98·7 (15·6)	101·4 (11·9)
$FEV_{0\cdot75}$	87·2 (14·2)	92·7 (15·0)	86·1 (15·2)**	94·8 (14·0)	98·4 (15·2)	101·5 (10·2)	96·3 (14·7)	101·9 (10·1)
MEF_{50}	78·6 (20·5)	88·7 (26·1)	78·9 (24·0)*	91·3 (25·4)	92·5 (21·3)	105·1 (23·5)	92·5 (20·3)*	105·3 (23·7)

FVC=forced vital capacity; $FEV_{0\cdot75}$=forced expired volume in 0·75 seconds; MEF_{50}=maximum expiratory flow at 50% of FVC. Because some of the questionnaires were not completely filled, full data were available in only 121 and 100 children in the low birthweight and the reference groups respectively.

Significance of difference between symptomatic and asymptomatic subjects by unpaired *t* test: *$p<0\cdot05$; **$p<0\cdot01$.

occurred *after* certain outcome indices, such as the presence or otherwise of idiopathic respiratory distress syndrome or bronchopulmonary dysplasia, were known. Their recruitment was therefore susceptible to bias. Symptomatic subjects or those who have more severe neonatal respiratory illness are often more readily available and willing to participate in studies than are symptom free children. This study is unique in that we prospectively examined the lung function of the survivors of an age specific and birthweight specific cohort of low birthweight children born within a 12 month period, irrespective of neonatal respiratory illness.

Both of the neonatal units participating in this study were neonatal referral centres; 28% of the low birthweight subjects in our study were outborn, mainly in local hospitals. Consequently our overall findings might be slightly biased towards those with more severe neonatal respiratory illness.

Our reference population was unselected and apart from age, matching was not sought. It comprised more children of ethnic minorities (low birth weight 22% compared with reference 44%) and those whose parents were either unskilled or unemployed (low birth weight 19% compared with reference 42%). Adjustment for differences in ethnic background on lung function was made using multiple regression analysis (table 1). There was no association between airway function and socioeconomic status in either group of children.

In addition to the 30 low birthweight children who were inaccessible for legitimate reasons (emigration, loss to follow up, etc), an additional 52 subjects in the cohort did not attend our lung function sessions. Two thirds of them lived outside Greater London. There was no difference between those who attended and those who did not with respect to ethnic origin, birth weight, gestational age, and the level of neonatal respiratory treatment received, although 13 of the 23 who had emigrated since discharge were non-white. Their omission was unlikely to have influenced our results.

Neonatal death could have been an important source of bias. Out of the 292 live births and admissions in the cohort, 76 died. If survival were associated with inherently better lung function, then differences in survival rates between different neonatal units, differences in the type of infant population served and the era in which study subjects were born will all add to the difficulties in comparing published studies of lung function in children of low birth weight.

REFERENCE VALUES FOR LUNG FUNCTION

We compiled our own reference values for three important reasons. Firstly, all standards of lung function published so far are based on measurements collected from children with a wide range of ages, with either very few or no young children of an age close to that of our low birthweight cohort. The prediction equations compiled by these studies might be unreliable for young children. Secondly, although ethnic differences on lung function are well known,[23] most prediction equations published so far apply to white children alone. As 22% of our low birthweight cohort was non-white, such prediction equations might not be appropriate. Indeed, we too observed significant differences in lung function for height related to ethnic background. The differences observed by us were almost identical to those recently reported in a large sample of non-white children in south London.[24] Thirdly, by deriving prediction equations from our own reference populations recruited irrespective of their previous respiratory history or environmental and social background, unlike those of previous studies which compared their findings with 'normal' controls, we could be certain that our findings were not biased.

LUNG FUNCTION IN CHILDREN OF LOW BIRTH WEIGHT

The low birthweight children had poorer forced expiratory flow indices than the reference group with a well preserved vital capacity. In simple terms, this implies 'obstructive' disease suggestive of airway dysfunction, rather than a 'restrictive' disorder. Airway dysfunction could be a consequence of a multitude of factors such as abnormal intrauterine development, preterm birth, and neonatal respiratory illness or its treatment (fig 3). In addition, host factors of genetic origin could directly determine airway function (explaining, for instance, sex and ethnic differences) as well as influencing individual vulnerability to adverse

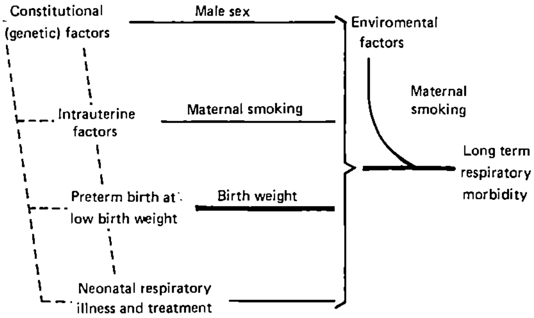
Constitutional (genetic) factors
Male sex
Enviromental factors
Intrauterine factors
Maternal smoking
Maternal smoking
Long term respiratory morbidity
Preterm birth at low birth weight
Birth weight
Neonatal respiratory illness and treatment

Fig 3 *Model of the aetiology of chronic respiratory morbidity. The strength and nature of significant associations that were estimated from the results of the present study are indicated by the width of the lines. Dotted lines represent hypothetical associations.*

environmental factors during infancy and childhood. Male sex was a risk factor of the latter type. The size of this study was not sufficiently large to enable us to determine the relative importance of all these factors with respect to outcome. It did allow us to test the hypothetical association between neonatal respiratory treatment and long term airway function as well as to examine some of the more important factors.

In previous studies, which examine the long term consequences of neonatal respiratory illness and its treatment but without simultaneous examination of preterm children who did not require treatment,[14-16] it has been assumed that the findings were due to airway 'damage' sustained in the neonatal period. Contrary to such an assumption, our study provided clear evidence for a strong association between airway function and birth weight irrespective of neonatal respiratory illness (fig 2). Two previous studies that included a healthy low birthweight control group, have also found poorer airway function with and without neonatal respiratory illness,[10 13] although these studies were too small to allow for correlation analysis. In contrast with two other studies,[16 25] we were unable to find any association between oxygen score or duration of mechanical ventilation and subsequent airway function in those who received neonatal respiratory treatment. In one of these studies the subjects were probably highly selected, as evidenced by an extraordinarily low mean forced expired volume in one second for the group with respiratory distress syndrome (70% of predicted).[25] In our cohort, the mean $FEV_{0·75}$ for the mechanically ventilated group and the group with bronchopulmonary dysplasia was 88·8% and 79·5% of predicted respectively. In the other study,[16] the authors' conclusions did not tally with their own earlier findings on the same subjects.[26] Their earlier report suggested that, although these children had abnormal lung mechanics in early infancy after neonatal mechanical ventilation, most of them had returned to normal by 0·5 to 1·5 years. At the age of 9, these children had abnormal airway function that correlated with the duration of mechanical ventilation. It is difficult to reconcile these conflicting results.

The fact that poorer airway function was observed in the very low birthweight children who did not require any form of neonatal respiratory treatment was not due to their smaller size at 7 years. Their body dimensions and FVC were not significantly different from the remainder of the cohort. It is possible that airway growth might be more vulnerable than peripheral lung growth to the adverse effects of very premature birth. Conducting airways and air spaces have a complex embryonic origin.[27 28] The lungs are only partially developed at term.[29 30] Multiplication of alveoli takes place in late fetal life as well as postnatally.[31] Thereafter growth in lung volume is mainly due to increase in their size. It has been suggested that the wide between subject variability in maximum expiratory flow volume curves in healthy subjects is the result of variation in the development of airways in relation to their air spaces.[28 32] This is termed dysanaptic growth. It is possible that very premature birth that disrupts the normal process of lung growth and development could in some way alter the integrated pattern of growth of the airways and the air spaces. There is as yet no histological study that examines the effect of premature birth itself on the growth of the conducting airways.

The male sex was found to be associated with poor airway function in the low birthweight cohort. In addition, more boys had neonatal respiratory illness and required mechanical ventilation than girls. They also had a slightly poorer survival rate (72% compared with 78%, inborn and outborn combined). There appears to be a striking parallel between our findings and the observation that respiratory illnesses are commoner in boys during childhood.[33 34] The male sex might indeed be constitutionally more vulnerable to neonatal respiratory illness and adverse environmental influence.

Maternal smoking, but not smoking by other members of the household, was independently associated with reduction in expiratory flow indices. Such a specific association was not surprising as it has also been observed in larger populations of children.[35-37] Among all members of the household, mothers are the ones with the most intimate contact with their children. It is, however, surprising that such an effect was detectable in a study as small as ours, as it might be assumed that the effects of neonatal mechnical ventilation and oxygen treatment would be greater than that of cigarette smoke exposure. In the reference group, though children whose mothers smoked also had lower MEF_{75}, the difference was not significant ($p=0·17$). Evidence is accumulating to suggest that the effects of maternal smoking on the respiratory health of their children occur antenatally.[38] As 92% and 79% of the current maternal smokers were smokers before and during their pregnancy respectively, it was not possible to determine, within the size of our cohort, whether the effect of maternal smoking was fetal or postnatal.

OUTCOME FOR BABIES WITH CHRONIC OXYGEN DEPENDENCY (BRONCHOPULMONARY DYSPLASIA)

The subgroup with bronchopulmonary dysplasia had reduced vital capacity as well as other airway function indices. We do not know whether the reduced FVC was a consequence of restrictive lung disease or of airway obstruction. Their $FEV_{0\cdot75}$: FVC ratio was no different from that of the remainder of the cohort (fig 1) and they had no evidence of chest hyperinflation, suggesting that their lungs might be small. There is good morphological data on lung structure in bronchopulmonary dysplasia. Hislop *et al* found evidence of damage to alveoli (that is, thickened interalveolar septa with increased elastic and fibrous tissue, dilatation of alveolar ducts, and overblown alveoli) in typical cases of bronchopulmonary dysplasia and to a lesser extent in those who required only minimal positive pressure mechanical ventilation.[39] Such damage might adversely affect lung growth, leading to continued abnormalities in early infancy.[40 41] As alveolar development is thought to be completed by about 2 years of age,[31] complete catch up growth seems unlikely. Indeed severe reduction in the number of alveoli has been observed in cases of bronchopulmonary dysplasia.[39 42] Alveolar underdevelopment could be an explanation for the small FVC in our survivors who had bronchopulmonary dysplasia. Without knowing the lung size of these infants before neonatal respiratory treatment began, it is a matter of conjecture as to whether the reduction in FVC in these children was a consequence of lung damage resulting from neonatal respiratory support, or whether they had constitutionally smaller lungs than other low birthweight children to begin with, thus accounting for the high level of respiratory treatment that they required in the neonatal period.

In other studies in which pulmonary hypoplasia is suspected in the neonatal period, however, catch up in the growth of lung function seems to occur by the second year of life.[43] The fact that our subjects had grossly abnormal lung function at the age of 7 years implies additional pathological processes.

As in most other series, bronchopulmonary dysplasia occurred exclusively in very low birthweight subjects (less than 1500 g) who required neonatal mechanical ventilation. There was, however, no association between the severity of the initial respiratory illness or the peak inspiratory pressure used and the development of bronchopulmonary dysplasia. Some of those who developed bronchopulmonary dysplasia had relatively mild respiratory illness initially. Six did not require mechanical ventilation in the first 48 hours. Four children did not have respiratory distress syndrome, but were ventilated for respiratory insufficiency and recurrent apnoea. Six children required a maximum inspiratory pressure of only 16 cm H_2O or less. In four, the maximum concentration of oxygen given had never exceeded 60%. In contrast, many infants who had severe respiratory distress syndrome and required a high level of oxygen treatment and mechanical ventilation from birth did not progress to develop bronchopulmonary dysplasia.

These findings imply that the children with bronchopulmonary dysplasia might be more vulnerable to the adverse effects of neonatal respiratory treatment. Instead of attributing the poorer airway function in such children to oxygen toxicity or to the effects of barotrauma on immature lungs, our contention is that these children might have had a more vulnerable respiratory system than other very low birthweight children to begin with. Whether the origins of this situation should be sought in fetal life or in the early neonatal period, we cannot tell.

Neonatal complications such as air leak could be important determinants of long term outcome, but because there were only eight survivors who had this particular complication, of whom only five were able to participate in lung function tests, the number was too small to allow for a statistical evaluation. Other putative risk factors such as patent ductus arteriosis and necrotising enterocolitis were also too rare for evaluation.

CLINICAL IMPORTANCE OF REDUCED AIRWAY FUNCTION

The strong association between cough and reduction in airway function confirmed the clinical significance of our findings. Within the limitations of our snap shot observations, it is not possible to say whether the reduced airway function observed in these children at 7 years represented the 'end-point' in the development of the lungs. The implications for the development of chronic airflow obstruction in later adult life are unknown. Over the previous few years there had been a progressive reduction in respiratory symptoms in the cohort. From 7 years to adulthood, although lung units do not increase numerically, the FVC increases by as much as 2·5 to 3 fold.[27] Only longitudinal measurements collected in subsequent years will enable us to determine whether or not the airway function of the low birthweight cohort will show catch up growth and attain a level comparable with the general population.

The implications for prevention are not as clear as one might wish. Firstly, we were unable to show a 'dose-effect' association between neonatal respiratory treatment and childhood lung function. Maternal smoking is the only factor that is potentially amenable to manipulation. Our evidence, added to the formidable published data,[38 44] adds weight to efforts to reduce cigarette consumption by expectant mothers and families with young children.

More difficult to achieve, but potentially far greater in its benefits, would be a reduction in preterm birth. In babies of very low birth weight who are at greatest risk, it will be important to identify those factors that predispose to chronic oxygen dependency, bronchopulmonary dysplasia, and subsequent respiratory dysfunction. It is in this group that the greatest returns are to be expected for future investment in research.

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References

[1] O'Brodovich HM, Mellins RB. Bronchopulmonary dysplasia: unresolved neonatal acute lung injuries. *Am Rev Respir Dis* 1985;**132**:694–709.

[2] Smyth JA, Tabachnik E, Duncan WJ, *et al.* Pulmonary function and bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia. *Pediatrics* 1981;**68**:336–40.

[3] Berman W Jr, Katz R, Yabek SM. Long-term follow-up of bronchopulmonary dysplasia. *J Pediatr* 1986;**109**:45–50.

[4] Bader D, Ramos AD, Lew CD, *et al.* Childhood sequelae of infant lung disease: exercise and pulmonary function abnormalities after bronchopulmonary dysplasia. *J Pediatr* 1987;**110**: 693–9.

[5] Lamarre A, Linsao L, Reilly BJ, *et al.* Residual pulmonary abnormalities in survivors of idiopathic respiratory distress syndrome. *Am Rev Respir Dis* 1973;**108**:56–61.

[6] Bryan MH, Levison H, Swyer PR. Pulmonary function in infants and children following the acute neonatal respiratory distress syndrome. *Bull Eur Physiopathol Respir* 1973;**9**: 1587–600.

[7] Dinwiddie R, Mellor DH, Donaldson SHC, Tunstall ME, Russell G. Quality of survival after artificial ventilation of the newborn. *Arch Dis Child* 1974;**49**:703–10.

[8] Heldt GP, McIlroy MB, Hansen TN, *et al.* Exercise performance of the survivors of hyaline membrane disease. *J Pediatr* 1980;**96**:995–9.

[9] Stahlman M, Hedvall G, Lindstrom D, *et al.* Role of hyaline membrane disease in production of later childhood lung abnormalities. *Pediatrics* 1982;**69**:572–6.

[10] Coates AL, Bergsteinsson H, Desmond K, *et al.* Long-term pulmonary sequelae of premature birth with and without idiopathic respiratory distress syndrome. *J Pediatr* 1977;**90**: 611–6.

[11] Coates AL, Desmond K, Willis D, *et al.* Oxygen therapy and long-term pulmonary outcome of respiratory distress syndrome in newborns. *Am J Dis Child* 1982;**136**:892–5.

[12] Borkenstein J, Borkenstein M, Rosegger H. Pulmonary function studies in long-term survivors with artificial ventilation in the neonatal period. *Acta Paediatr Scand* 1980;**69**:159–63.

[13] Mansell AL, Driscoll JM, James LS. Pulmonary follow-up of moderately low birthweight infants with and without respiratory distress syndrome. *J Pediatr* 1987;**110**:111–5.

[14] Reidel F. Long-term effects of artificial ventilation in neonates. *Acta Paediatr Scand* 1987;**76**:24–9.

[15] Driscoll DJ, Kleinberg F, Heise CT, *et al.* Cardiorespiratory function in asymptomatic survivors of neonatal respiratory distress syndrome. *Mayo Clin Proc* 1987;**62**:695–700.

[16] Andréasson B, Lindroth M, Mortensson W, Svenningsen NW, Jonson B. Lung function eight years after neonatal ventilation. *Arch Dis Child* 1989;**64**:108–13.

[17] Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Aber VR. Airway responsiveness in low birthweight children and their mothers. *Arch Dis Child* 1988;**63**:905–10.

[18] Chan KN, Elliman A, Bryan EM, Silverman M. Respiratory symptoms in children of low birth weight. *Arch Dis Child* 1989;**64**:1294–304.

[19] Chinn DJ, Cotes JE. Transit time analysis of spirograms: which blow is best? *Bull Eur Physiopathol Respir* 1986;**22**:461–6.

[20] Cole TJ. Linear and proportional regression models in the prediction of ventilatory function. *Journal of the Royal Statistical Society* 1968;**131**:280–302.

[21] Quanjer PH, ed. Standardised lung function testing. Report of the working party on standardisation of lung function. European Community for Coal and Steel, Luxembourg. *Bull Eur Physiopathol Respir* 1983;**19** (suppl 5):1–95.

[22] Baker RJ. *The GLIM system: release 3.* London: Royal Statistical Society, 1978.

[23] Cotes JE. *Lung function assessment and application in medicine.* 4th ed. Oxford: Blackwell Scientific Publications, 1979.

[24] Johnston IDA, Bland JM, Anderson HR. Ethnic variation in respiratory morbidity and lung function in childhood. *Thorax* 1987;**42**:542–8.

[25] Bertrand JM, Riley SP, Popkin J, *et al.* The long-term pulmonary sequelae of prematurity: the role of familial airway hyper-reactivity and respiratory distress syndrome. *N Engl J Med* 1985;**312**:742–5.

[26] Lindroth M, Mortensson W. Long-term follow-up of ventilator treated low birthweight infants. *Acta Paediatr Scand* 1986;**75**: 819–26.

[27] Inselman LS, Mellins RB. Growth and development of the lung. *J Pediatr* 1981;**98**:1–15.

[28] Green M, Mead J, Turner J. Variability of maximum expiratory flow-volume curves. *J Appl Physiol* 1974;**37**:67–72.

[29] Hislop A, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. *Early Hum Dev* 1986;**13**:1–11.

[30] Langston C, Kida K, Reed M, *et al.* Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis* 1984;**129**: 607–13.

[31] Thurlbeck WM. Postnatal human lung growth. *Thorax* 1982;**37**: 564–71.

[32] Mead J. Dysanapsis in normal lungs assessed by the relationship between maximum flow, static recoil and vital capacity. *Am Rev Respir Dis* 1980;**121**:339–42.

[33] Williams HE, Phelan PD. *Respiratory illness in children.* Oxford: Blackwell Scientific Publications, 1975.

[34] Glezen WP, Denny FW. Epidemiology of acute low respiratory disease in children. *N Engl J Med* 1973;**288**:498–505.

[35] Tashkin DP, Clark VA, Simmons M, *et al.* The ULCA population studies of chronic obstructive respiratory disease. VII Relationship between parental smoking and children's lung function. *Am Rev Respir Dis* 1984;**129**:891–7.

[36] Vedal S, Schenker MB, Samet JM, *et al.* Risk factors for childhood respiratory disease: analysis of pulmonary function. *Am Rev Respir Dis* 1984;**130**:187–92.

[37] O'Connor GT, Weiss ST, Tager IB, *et al.* The effect of passive smoking on pulmonary function and non-specific bronchial responsiveness in a population-based sample of children and young adults. *Am Rev Respir Dis* 1987;**135**:800–4.

[38] Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch Dis Child* 1987;**62**:786–91.

[39] Hislop A, Wigglesworth JS, Desai R, *et al.* The effects of preterm delivery and mechanical ventilation on human lung growth. *Early Hum Dev* 1987;**15**:147–64.

[40] Stocks J, Godfrey S, Reynolds EOR. Airway resistance in infants after various treatments for hyaline membrane disease: special emphasis on prolonged high levels of inspired oxygen. *Pediatrics* 1978;**61**:178–83.

[41] Wong YC, Beardsmore CS, Silverman M. Pulmonary sequelae of neonatal respiratory distress in very low birthweight infants: a clinical and physiological study. *Arch Dis Child* 1982;**57**:418–24.

[42] Sobonya RE, Logvinoff MM, Taussig LM, *et al.* Morphometric analysis of the lung in prolonged bronchopulmonary dysplasia. *Pediatr Res* 1982;**16**:969–72.

[43] Helms P, Stocks J. Lung function in infants with congenital pulmonary hypoplasia. *J Pediatr* 1982;**101**:918–22.

[44] Simpson RJ, Smith NGA. Maternal smoking and low birthweight: implications for antenatal care. *J Epidemiol Community Health* 1986;**40**:223–7.

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Respiratory symptoms in children of low birth weight

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SUMMARY We recorded the respiratory history by questionnaire in a 7 year old cohort of children whose birth weight was under 2000 g and an unselected reference group of local schoolchildren of the same age. Complete data were obtained in 121 low birthweight children (90% of those studied): 62 who had no neonatal respiratory illness, 25 who had oxygen treatment only, and 34 who received mechanical ventilation (of whom 10 had bronchopulmonary dysplasia). The low birthweight children were no more likely to wheeze than the reference group, but frequent and troublesome cough was significantly more common, especially among children of very low birth weight (under 1500 g) who had received neonatal respiratory treatment. Neonatal mechanical ventilation was not associated with increased symptoms when compared with neonatal oxygen treatment alone. The prevalence of cough at the age of 7 was independently associated with the level of neonatal intensive care as defined by oxygen score. Although there was no excess of wheeze in the cohort compared with the reference group, there was a weak correlation between wheeze and the neonatal oxygen score as well as with maternal smoking. Loss of schooling due to respiratory symptoms in the nine months before this study was no greater in children of low birth weight than in the reference group.

The literature contains a remarkable lack of information on the long term respiratory symptoms that are experienced by children of low birth weight. Our knowledge is based on a number of retrospective studies designed primarily to evaluate lung function. These studies concern small, heterogeneous groups of survivors selected on the basis of a number of different criteria. It is nevertheless fairly well established that respiratory illness and chest symptoms are common in the first year of life in those who survive neonatal respiratory distress syndrome.[1–7] The severity of these early symptoms appears to be related to the intensity of respiratory treatment in the neonatal period.[7 8] During the first year most of the survivors improve rapidly in respect of both clinical features and lung function,[7 9] so that by school age, children are generally symptom free and are presumed to have recovered completely.[10–12] These conclusions are based for the most part on studies that were carried out at a time when there were relatively few long term very low birthweight survivors. Recently, with increased survival of very small infants, a number of studies have shown abnormal airway function at school age.[13–15]

Little is known, however, of the clinical importance of these physiological findings as very few authors have attempted to relate their measurements to symptoms. Those who have done so have been concerned only with whether or not the subjects were 'symptomatic' in comparison with either 'normal' or 'historical' controls rather than with a truly representative random sample of children from the general population who were born at the same time. In addition, most studies have dealt with the outcome in highly selected groups of subjects with, for instance, respiratory distress syndrome or bronchopulmonary dysplasia. There is no published study that has systematically examined the long term respiratory morbidity of prematurely born children with and without neonatal respiratory illness.

The present study had two specific objectives. Firstly, we aimed to examine the long term respiratory morbidity in a cohort of age specific and birthweight specific low birthweight children (less than 2000 g) at the age of 7 years and to compare them with an unselected reference population of local schoolchildren of the same age. Secondly, we wished to test the hypothesis that respiratory symptoms in the low birthweight children, if present, were a consequence of neonatal respiratory illness and its treatment.

Subjects and methods

SUBJECTS

Details of the low birthweight cohort and the reference group of children have already been described.[16] Briefly, of the 292 infants of under 2000 g birth weight who were admitted to the neonatal units of Hammersmith and Queen Charlotte's Maternity Hospitals in the 12 month period (June 1979–May 1980), 216 were alive at 7 years. Of these, 134 were seen and examined, although not all were capable of completing the lung function tests. A group of 123 unselected local schoolchildren born in the same period was examined concurrently with the low birthweight cohort and formed the reference group. Children were selected from the register of three local schools on the basis of their date of birth, irrespective of their social and family background. No subject was excluded on the basis of current symptoms, or of a personal or family history of respiratory illness.

Perinatal data on the low birthweight children had been recorded at the time of discharge from the neonatal units. From this file, we extracted information on a whole range of features that might have value as predictors of respiratory symptoms later in childhood. Among many factors, these included birth weight, gestational age, presence of neonatal respiratory illness and its complications, duration of oxygen and mechanical ventilation treatment, peak inspiratory ventilator pressure used, and maternal cigarette consumption during pregnancy.

The studies were approved by local ethics committees and the education authority. Informed consent was obtained from parents of both the low birthweight cohort and the local schoolchildren.

PROTOCOL

Identical questionnaires were used to record clinical, social, and family history for the low birthweight cohort and the reference population. (A copy of the questionnaire can be obtained from the corresponding author.) The low birthweight children were seen in hospital lung function clinics together with their parents. We were unable to obtain their clinical history by direct interview. On the other hand, the reference children were seen at school without their parents, who were therefore asked to complete both a consent form and a questionnaire at home and to return them to the school. In the questionnaire we asked if the child had symptoms of cough and wheeze, if the symptoms occurred occasionally or frequently, if the child had previously had treatment or had been in hospital for chest illness and if any members of the close family (natural parents and siblings) had asthma, hay fever, or eczema. We asked about the occupation and the average number of cigarettes currently consumed per day by each parent. Information on home condition, such as the type of fuel used for cooking and heating, if the home was cold or damp, and if any pets were kept, was also sought. We recorded whether the child had had a cold within the previous four weeks.

Even though the same questions were asked, we could not be certain about the comparability of the questionnaire responses in the two populations of children, as the methods used, interview or self administration, were different. For this reason, at the end of our study parents of all the children in the study were asked to complete a second self administered questionnaire, which was again identical for both groups of children. Those for the low birthweight cohort were sent by mail, whereas those of the reference group were delivered by their class teachers. This questionnaire allowed us to determine repeatability and to ask a few additional questions.

In order to improve its return rate, questions concerning parental social class and home conditions were omitted from the second questionnaire. Instead, further details of current symptoms were sought and questions concerning previous chest infections, admissions to hospital, atopic diathesis (asthma, hay fever, and eczema) in the family, and parental cigarette consumption were repeated. We also asked if smoking habits had changed in the previous few months. The second questionnaire was administered at the same time for both groups of children. In order to ensure that the questionnaire was completely filled, the parents were asked to indicate those questions that they did not understand or could not answer. The mean time interval between the two questionnaires for the low birthweight children was about five months whereas for the reference group it was three months. A final total of 95% and 89% of the questionnaires were returned by the parents of the low birthweight and reference groups respectively. To ensure comparability between low birthweight cohort and the reference population, the second questionnaire formed most of the data base for this analysis. Only the parents' occupation and home conditions were based on the first questionnaire.

Lung function and bronchial responsiveness to histamine were measured on all children who did not have a recent respiratory infection. Details are described elsewhere.[16] Skin prick tests against common allergens, namely house dust mite, group B pollens, and cat fur together with a control solution (Bencard) were carried out on the low birthweight children only. Subjects were considered atopic when a weal of at least 2 mm in diameter was present in response to any one of the three allergens in the absence of a similar response to the control solution.

DEFINITIONS OF RESPIRATORY SYMPTOMS AND ILLNESSES

Wheeze and cough, whether they occurred unprovoked or in association with common colds or with exercise were ascertained separately. 'Wheeze with colds' was defined as a positive response obtained to both the questions 'Has your child ever had wheezy chest (whistling noise) with common colds?' and 'If yes, does it happen frequently?' Wheeze with exercise was defined as an affirmative response to the question 'Does exercise make his/her chest wheezy?' Those children in whom a positive response was obtained for both of the questions 'Has he/she ever had troublesome cough following common colds' and 'If yes, does it happen frequently?' were referred to as having 'troublesome cough with colds'. Those in whom a positive response was obtained to the question 'Does exercise make him/her cough?' were considered to have 'cough with exercise'. Children whose parents answered 'Yes' to both of the questions 'Does he/she cough at night not due to colds?' and 'If yes, does it happen frequently?' were considered to have 'frequent nocturnal cough'. Wheeze and daytime and nocturnal cough were considered separately.

Previous respiratory illnesses were defined as an affirmative response to a series of questions of the form 'Has he/she ever had (i) asthma (ii) whooping cough (iii) croup (stridor) (iv) chest infection (v) an admission to hospital because of chest trouble?' The age at which each of these first occurred and the number of episodes of each were also asked. A family history of eczema, hay fever, and asthma was sought among first degree relatives (natural parents and siblings). Parents who were current smokers and lived in the same household as the subjects were defined as current smokers.

STATISTICAL ANALYSIS

The extent of agreement between the responses to identical questions in the two questionnaires was determined by the index of repeatability, known as the Cohen's kappa ($\varkappa$).[17] This index takes into account the chance agreement that could have occurred in certain questions to which a positive response is low.

Respiratory outcome at 7 years was examined by dividing the low birthweight cohort into subgroups according to birth weight (above or below 1500 g) and the presence or absence of respiratory illness in the neonatal period. 'No neonatal respiratory illness' was defined as the absence of respiratory signs or as the need for oxygen treatment at a concentration of no more than 40% for no more than six hours. 'Oxygen only' was defined as neonatal respiratory illness needing oxygen treatment of over 40% or for over six hours but mechanical ventilation, if any, for less than three hours. 'Mechanical ventilation' was defined by the need for over three hours' mechanical ventilation. An oxygen dependent group of 10 children with bronchopulmonary dysplasia was defined by their oxygen dependency at 30 days of postnatal age. All 10 weighed under 1500 g at birth and had required mechanical ventilation (mean duration of 311 hours, range 18 to 916).

In order to examine the association between long term symptomatology and the level of neonatal intensive treatment, an oxygen score that reflected both the duration and intensity of treatment in the neonatal period was computed. This was derived by allocating one point for each hour of oxygen treatment with an inspired oxygen concentration between 22% and 40%, two points for each hour between 41 and 60%, three points for each hour between 61 and 80%, and four points for each hour between 81 and 100%.

Crude examination of the association between perinatal and other risk factors and long term symptomatology was initially analysed using χ^2 tests. For convenience the symptoms were considered present if they were reported to be still frequent, irrespective of whether they occurred unprovoked or after colds. Wheeze and cough were considered separately. As no allowance had been made for multiple tests performed, it was therefore prudent to accept a p value of $<0{\cdot}01$ as indicative of statistical differences between groups.

Multiple logistic regression analysis was used to test the hypothetical association between symptoms and perinatal factors allowing for other factors that might also influence the occurrence of symptoms. Generalised linear interactive modelling was adapted for such analysis.[18]

Results

REPEATABILITY OF QUESTIONNAIRES

Some of the questionnaires were not completely filled. Consequently complete data were available in 121 (90%) and 100 (81%) of the children in the low birthweight and reference groups who attended. Only those subjects with complete information have been included in the following analysis. The overall agreement between the first and second questionnaire within the low birthweight and the reference groups was no different but the $\varkappa$ values were generally higher for the low birthweight cohort (table 1). Questions about asthma were significantly

Table 1 *Repeatability of responses to comparable questions in the two questionnaires administered to the parents of 121 low birthweight and 100 reference children*

	Proportion in agreement		*Index of repeatability* (κ)*	
	Low birthweight	*Reference*	*Low birthweight*	*Reference*
Previous hospitalisation	0·96	0·97	0·86	0·75
Cigarette consumption by father†	0·92	0·84	0·77	0·65
Cigarette consumption by mother†	0·94	0·96	0·85	0·90
Asthma in subjects	0·98	0·94	0·91§	0·72
Family history:‡				
Asthma	0·99	0·96	0·88§	0·71
Eczema	0·94	0·96	0·53	0·65
Hay fever	0·95	0·94	0·75	0·65

*Cohen's kappa (κ) is defined as the observed agreement in excess of that expected as a proportion of the total excess agreement that is possible.
†Agreement defined as within 20% of daily mean.
‡Natural parents and siblings.
§Significance of difference between groups by z test: $p<0·01$.

more consistently answered by parents of the low birthweight cohort.

FAMILY, HOME, AND ENVIRONMENTAL BACKGROUND

There was no difference in the atopic background between the low birthweight and the reference group, as evidenced by the similarity in the prevalence of familial asthma and hay fever (table 2).

More mothers than fathers were current smokers in both groups. This was in part due to the fact that mothers only were present in the many single parent households, although the prevalence of maternal smoking remained higher than that of paternal smoking even when making allowance for this factor. There was, however, no difference in the prevalence of current maternal smoking between the two groups. The parents of the reference group were of lower socioeconomic status (defined as unskilled or unemployed). The fact that there were more single mothers in the reference group who were not in any form of employment contributed to much of the difference. A greater proportion of fathers of reference children were smokers. There was, however, no significant difference in adverse environmental factors, such as reported poor housing and use of gas cooking at home.

Table 2 *Family, environmental, and social background in the low birthweight and the reference group at 7 years. Results are No (%)*

	Low birthweight (n=121)	*Reference (n=100)*
Asthma in either parent	13 (11)	13 (13)
Asthma in close family*	20 (17)	18 (18)
Hay fever in either parent	34 (28)	30 (30)
Hay fever in close family*	38 (31)	35 (35)
Father a current smoker	27 (22)**	36 (36)
Mother a current smoker	39 (32)	43 (43)
Home cooking with gas stove	80 (66)	69 (69)
Home cold or damp	18 (15)	21 (21)
Low socioeconomic status†	23 (19)***	42 (42)
Single parent family	14 (12)	18 (18)

*Included natural parents and siblings.
†Parents who were either unskilled or unemployed.
Significance of difference between groups by χ^2 test: **$p<0·01$; ***$p<0·001$.

HISTORY

A history of asthma was similar in the two groups of children (table 3). This is consistent with the fact that a family history of asthma was no more common in the low birthweight cohort than in the reference group (table 2).

A history of whooping cough, previous chest infection, and a previous admission to hospital for

Table 3 *Respiratory history obtained at 7 years in the low birthweight and the reference group. Results are No (%)*

	Low birthweight (n=121)	*Reference (n=100)*
Asthma	13 (11)	13 (13)
Whooping cough	29 (24)*	11 (11)
Croup (stridor)	13 (11)	4 (4)
Previous chest infections	19 (16)*	7 (7)
Previous hospitalisation for chest illness	24 (20)*	8 (8)

Significance of difference between groups by χ^2 test: *$p<0·05$.

chest illness was twice as common in the low birthweight cohort as in the reference group (p<0·05). Because the low birthweight children had been seen at special follow up clinics since birth, we were able to establish that 74% and 75% of the reported chest illnesses and admissions to hospital respectively had been documented in the first 2 years of life. The prevalence of chest infection recorded during the first 2 years was 2%, 20%, 18%, and 30% for children who had no neonatal respiratory illness, oxygen treatment only, mechanical ventilation, and bronchopulmonary dysplasia, respectively. For admission to hospital for respiratory illness, the figures were 6%, 12%, 18%, and 40%, respectively. In the nine months before the study there was no significant difference in the loss of schooling due to respiratory illness between the low birthweight and the reference group (mean loss of schooling: low birth weight 4·7 days, reference 3·8 days).

Table 4 *Respiratory symptoms in the low birthweight cohort and the reference group at 7 years. Results are No (%)*

	Low birthweight (n=121)	*Reference (n=100)*
Wheeze with exercise unrelated to colds	13 (11)	9 (9)
Wheeze with or without colds	19 (16)	16 (16)
Cough with exercise unrelated to colds	26 (22)*	10 (10)
Cough with or without colds	41 (34)**	17 (17)
Frequent nocturnal cough unrelated to colds	11 (9)	8 (8)

Significance of difference between groups by χ^2 test: *p<0·05; **p<0·01.

CURRENT SYMPTOMS

The overall prevalence of wheeze, whether or not it occurred in association with common colds or with exercise, was similar in the low birthweight cohort and in the reference group (table 4). The prevalence of daytime cough was twice as common in the low birthweight subjects, though the prevalence of frequent nocturnal cough was almost identical. The overall prevalence of symptoms (all categories combined) in the low birthweight children was only marginally higher than that of the reference group (p=0·05).

In the reference group wheeze, but not cough, was significantly associated with a history of asthma in the family (p<0·01) (table 5). Daytime cough (but not nocturnal cough) was weakly associated with maternal smoking (p<0·05) but not with smoking by other members in the household. There was, however, no 'dose-effect' association between the number of cigarettes that mothers smoked per day and wheezing. There was no association between symptoms and the sex, or ethnic or socioeconomic background of the children. Gas cooking and poor housing (cold or damp) were not associated with increased symptoms in the children.

In contrast, in the low birthweight cohort, the association between wheeze and a family history of asthma did not reach a level of significance (p=0·06) and there was no association between the symptom and positive skin prick tests. There was, however, a significant association between maternal smoking and wheeze (p<0·01). For cough, when considered separately, there was a borderline association with both maternal smoking and low socioeconomic status (p<0·05), but, as will be seen later, these associations were not significant when other factors were taken into account. Smoking by other household members, sex, and ethnic background of the subjects were not associated with symptoms.

Table 5 *Prevalence of symptoms in relation to a family history of asthma, maternal smoking, and low socioeconomic status in the low birthweight and the reference group. Results are No (%)*

	Family history of asthma		*Maternal smoking*		*Low socioeconomic status†*	
	Yes	*No*	*Yes*	*No*	*Yes*	*No*
Wheeze:						
Low birth weight	6/20 (30)	13/101 (13)	11/39 (28)**	8/82 (10)	5/23 (22)	14/98 (14)
Reference	7/18 (39)**	9/82 (11)	9/43 (21)	7/57 (12)	6/42 (14)	10/58 (17)
Cough:						
Low birth weight	9/20 (45)	32/101 (32)	18/39 (46)*	23/82 (28)	12/23 (52)*	29/98 (29)
Reference	5/18 (28)	12/82 (15)	11/43 (26)*	6/57 (11)	9/42 (21)	8/58 (14)

Significance of association by χ^2 test: *p<0·05; **p<0·01.
(As no allowance has been made for multiple comparisons, the level of significance should be taken as p<0·01.)
†Parents who were either unskilled or unemployed.

Table 6 *Multiple logistic regression analysis for the association between neonatal oxygen score and respiratory symptoms at 7 years in the low birthweight cohort allowing for four pertinent variables*

Symptom variable	*Odds ratio*	*95% Confidence interval for odds ratio*	*Probability*
Wheeze:			
Family history of asthma	2·05	0·58 to 7·18	0·27
Atopic skin test	2·50	0·71 to 8·80	0·16
Maternal smoking	3·39	1·13 to 10·20	0·03
Low socioeconomic status	1·29	0·35 to 4·75	0·70
Neonatal oxygen score*	1·57	1·07 to 2·30	0·02
Cough:			
Family history of asthma	1·43	0·49 to 4·22	0·48
Atopic skin test	1·85	0·64 to 5·30	0·25
Maternal smoking	1·95	0·83 to 4·62	0·12
Low socioeconomic status	2·58	0·94 to 7·11	0·07
Neonatal oxygen score*	1·53	1·13 to 2·07	0·005

Definition: family history of asthma (negative=0, positive=1); atopic skin test (negative=0, positive=1); maternal smoking (no=0, yes=1); low socioeconomic status (no=0, yes=1).

*Defined in text: coded into five levels (as 0–4) for scores of 0, 1–60, 61–240, 241–960, 961–3800.

The magnitude of the estimated odds ratios is dependent on the integral values.

ASSOCIATION BETWEEN PERINATAL FACTORS AND CHILDHOOD SYMPTOMS

Wheeze was no more prevalent in the low birthweight children than in the reference group. Nevertheless there was a weak association between the prevalence of wheeze and both the neonatal oxygen score and maternal smoking (table 6).

The prevalence of cough in those who had no neonatal respiratory illness was no higher than in the reference group. It was, however, significantly higher in those who received neonatal respiratory treatment. The difference was largely attributable to the increase in the prevalence of cough in very low birthweight children (<1500 g) who had neonatal respiratory treatment (figure).

For those who required neonatal respiratory treatment, whether of very or moderately low birth weight (1501–2000 g), mechanical ventilation was not associated with an increase in symptoms at 7 years. The 10 children who were oxygen dependent beyond the neonatal period (those with bronchopulmonary dysplasia) had the highest prevalence of symptoms, but compared with other very low birthweight children without bronchopulmonary dysplasia, the difference was not significant.

The prevalence of asthma was extraordinarily low in the low birthweight children who received neonatal mechanical ventilation (5·9%), despite the fact that the prevalence of symptoms in those who received mechanical ventilation (wheeze 26·5%, cough 44%) was not different from those who received oxygen treatment alone (wheeze 24%, cough 40%). The prevalence of previous chest

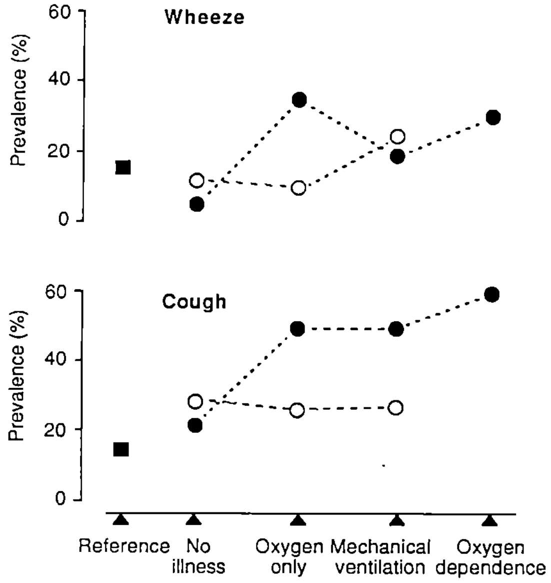

Figure *Prevalence of symptoms in the low birthweight and the reference groups in relation to neonatal respiratory treatment and birth weight. Reference group (n=100)=■; very low birthweight children (<1500 g)=●; and moderately low birthweight children (1501 to 2000 g)=○. Of the group of very low birthweight children, 22 had no neonatal respiratory illness, 40 oxygen treatment only, and 14 mechanical ventilation; the numbers for those of moderately low birthweight were 11, 16, and eight, respectively. There were 10 children in the oxygen dependent group, all of whom weighed <1500 g at birth.*

infections and admissions to hospital for chest illness in the low birthweight children who had no neonatal respiratory illness was equivalent to that of the reference group, but these features were commoner in those who had neonatal respiratory illness.

Using multiple logistic regression analysis the hypothetical association was confirmed between the level of neonatal intensive care (oxygen score) and symptoms reported at 7 years, allowing for a positive history of asthma in the family, positive skin tests, maternal smoking, and low socioeconomic status (table 6). There was no correlation between oxygen score and other variables considered in the analysis. Addition of variables that reflect the use and extent of neonatal mechanical ventilation, including both its duration and the peak inspiratory pressure required, did not explain any further deviance than oxygen score alone. In addition, the prevalence of wheeze was associated with maternal smoking, but not with any other perinatal factors examined, suggesting that both maternal smoking and oxygen score were independently associated with the symptom. Mothers who smoked were likely to have done so before (92%) and during (79%) pregnancy, therefore it was not possible to analyse the effect of maternal smoking during pregnancy and during infancy independently.

Discussion

SUBJECTS

Our study of childhood respiratory symptoms in low birthweight children has several features that contribute to avoid the bias inherent in most previous studies.

The study cohort was recruited into this prospective follow up study at the time of birth or entry into the neonatal units, and perinatal data were recorded at the time of discharge. Consequently their participation in the study was not influenced by the severity of their neonatal respiratory illness or their symptomatology later on in life. In addition, the cohort was recruited in a chronologically confined period of 12 months, and was drawn almost completely from the local population and immediately surrounding hospitals. There has only been one previous study that prospectively examined the respiratory symptomatology of prematurely born children,[8] but this did not extend beyond 1 year of age.

Matched full term controls were not recruited in the neonatal period. Instead, when lung function tests started, a random sample of local schoolchildren was recruited as the reference group. Recruitment was based simply on the geographical location of their schools and on their date of birth. No attempt was made to select subjects in order to match the low birthweight cohort. Children were not excluded from the reference group on the basis of their previous respiratory history or symptoms. Indeed symptom questionnaires were not analysed until lung function data had been collected from both groups of children. Because the reference group was unselected, some disparities in their background compared with that of the low birthweight cohort were to be expected. In the reference group there were more non-white children (low birthweight 22%, reference 44%) and parents were more commonly either unskilled or unemployed (low birthweight 19%, reference 42%), although the two groups had the same proportion of boys (low birthweight 53%, reference 54%). In contrast with a previous report, however, we found no association between symptoms and low socioeconomic status or ethnic group.[19] Such discrepancies did not affect our conclusions.

QUESTIONNAIRE

Two questionnaires were used to obtain the history for each child. The second self administered questionnaire, which was identical both in content and in method of administration to the parents of both groups of children, formed the main data base for this analysis. It was essential to ensure that both the questionnaire and the method of administration were identical because subtle changes in the wording of the questions could have influenced the response.[20]

The design of the second questionnaire was such that the questions were simple and most of the responses required a simple tick indicating 'yes' or 'no'. For most items the index of repeatability was high, suggesting that the questions were comprehended.

The questionnaire technique is not necessarily inferior to that of the interview technique in clinical research. The main disadvantage of the interview technique is that it is susceptible to observer bias. An interviewer who is aware whether the subject is in the study or control group may consciously or subconsciously probe harder for some responses while neglecting others. Such bias is probably common but is notoriously difficult to detect or to eliminate. It is important because it can substantially influence the findings of a study. The questionnaire method has the distinct advantage that if identical questionnaires are used and the mode of administration is similar, there is no room for observer bias.

In common with all clinical studies, a major uncertainty is recall bias by the respondents. Recent studies showing the lack of agreement between parental reports of recurrent sore throat compared with prospective monitoring,[21] between reported respiratory illness compared with general practitioners records,[22] and between diary scores of nocturnal cough compared with bedside tape recordings[23] illustrate how much care is needed to validate reports of symptoms and illness. Because our low birthweight cohort had been seen at intervals since their discharge from our neonatal units (follow up at 3, 6, 9, 12, 18 months and 2, 3, and 5 years), we were able to verify that 74% and 75% of chest infections and hospital admissions for chest illness had already been documented in the first two years. Conversely, of the 14 and 18 children who had documented chest infection and hospital admissions, only two and one respectively were not reported as such by parents at 7 years. The number of admissions to hospital reported at 7 years was highly correlated with those documented in previous years ($r=0{\cdot}96$). Our findings showed that misclassification due to parental failure to recall with respect to previous respiratory illnesses in the low birthweight cohort was small.

It was impossible to verify the reporting of such features as symptoms and cigarette consumption by parents. Accepting the fact that their verification was impracticable and probably technically impossible, we resorted to an alternative approach that was perhaps the next best. We examined the repeatability of the questionnaire responses. Although this did not test their validity, it reflected the general consistency of the responses obtained.

Although the same questions were asked and the overall repeatability compared favourably with other studies,[24] the repeatability of the responses ($\varkappa$ values) by the parents of the low birthweight children was in general better than that of the reference group. There are several possible explanations. Firstly, more parents of the reference group than the low birthweight cohort were of low socioeconomic status or from ethnic minorities. Secondly, the first questionnaire was administered to the parents of the low birthweight children by direct interview whereas that for the reference group was completed by the parents themselves without the assistance of an interviewer. Thirdly, the low birthweight children were recruited at or soon after the time of birth whereas the reference group was recruited at 7 years. The parents of the low birthweight cohort had been interviewed and questioned about their children's symptoms on a number of occasions in the previous years. This could enhance recall. The only way to avoid this form of bias would have been to recruit and subsequently monitor a concurrent full term control group. Finally, premature birth and its consequences may have heightened parental anxiety and influenced the perception and recollection of symptoms many years later. Such bias was unavoidable and would not be removed even if a parallel group of healthy full term children had been recruited and followed up from the time of birth.

The reporting of symptoms in young children is substantially different from that in the older populations as it takes place at second hand. Consequently reporting of symptoms is biased by differences in perception and recall in individual parents. The prevalence of wheeze was no greater in low birthweight than in reference children. This argues against a major recall bias in the parents of low birthweight children. Furthermore reliable responses to questions on symptoms can only be obtained if they are easily recognised. Hence questions concerning symptoms that were more subjective in nature, such as chestiness or shortness of breath on exercise were omitted. At appropriate places in our questionnaire, we asked if the parents would like to report any other symptoms. Five low birthweight children were reported to have shortness of breath compared with none in the reference group.

RESPIRATORY SYMPTOMS IN LOW BIRTHWEIGHT CHILDREN

Wheeze and cough are the commonest respiratory symptoms in children. They may occur with or without an associated cold. The symptoms were commonly reported even among the healthy reference population of schoolchildren: 17% had cough and 16% had wheeze (table 4). It is essential to compare the findings in low birthweight children with those of a large random sample extracted from the general population of children of the same age rather than with 'normal' controls. Ideally the study and the reference group should have been matched for all possible confounding variables. In our study, we opted for an unselected random sample of local schoolchildren as our reference group. There was an excess of children of non-white origin and lower socioeconomic status due to an excess of single parent families. If these factors had had any detectable adverse influence on respiratory health it would be to minimise the difference found between the two groups and would not affect our conclusions. In any case, in testing the hypothetical association between long term symptomatology and neonatal respiratory treatment, these were adjusted for by statistical techniques.

Despite the increasing survival of prematurely born infants, the amount of literature on the long term respiratory symptomatology in these children is surprisingly scanty. Various indices of respiratory morbidity had been used in previous studies. Some were based on clinical diagnosis, some based on lower respiratory tract infection with changes in chest radiographs[5] or requiring admission to hospital,[25 26] whereas others were concerned with wheeze.[3 27] Based on different criteria these studies, mostly reported in the 1970s, did not find increased wheeze or respiratory morbidity in prematurely born children or survivors of respiratory distress syndrome in childhood. It appeared, therefore, that complete recovery was the rule. These studies are difficult to interpret, however, as many of them did not include a matched control group.[5 6 27 28] Moreover, many of these studies were designed primarily to examine outcome by other techniques. Because of their small study size, these studies had poor statistical power to test for a difference between groups. Not surprisingly, therefore, respiratory symptoms in long term survivors were either mentioned in passing or omitted altogether by many previous investigators.

We found that low birthweight children were no more likely to wheeze than a random population of children of the same age. Nor was a history of asthma more common in low birthweight subjects or in their parents than in the reference group.[16] The major difference in symptoms between the low birthweight and reference population was in the prevalence of cough. The possibility that the increase in cough in the low birthweight cohort might have been due to better recall by their parents was not supported by any increase in wheeze in these children.

In addition to an increase in the prevalence of previous chest infections and hospital admissions, a history of whooping cough was also more common in the low birthweight children. This could be due to differences in pertussis vaccination rate as at the time there had been a reluctance to give such vaccinations to low birthweight children. Some of the 'frequent troublesome cough' in these children could have been attributed to whooping cough (pertussis syndrome).

ASSOCIATION BETWEEN RISK FACTORS AND LONG TERM SYMPTOMATOLOGY

In contrast with the reference group, in the low birthweight cohort there was a significant association between wheeze at 7 years and maternal smoking (table 6). A link between maternal smoking and the respiratory health of their children has previously been reported in epidemiological studies.[29–33] It is independent of many other confounding variables, and is probably a causal association that could be effected either postnatally or antenatally.[34 35] Within the relatively small study size of the low birthweight cohort (n=121), it was not possible to determine which of these was the case, as less than 20% of mothers who smoked altered their smoking habits in relation to pregnancy.

The lack of a significant association between wheeze and a positive family history of asthma in the low birthweight cohort is surprising given the strength of the association in the reference group (table 5). It suggests that other factors were predominant, and that our study was too small to enable us to detect an additional familial factor. Although there was no excess of wheeze in the low birthweight children compared with a random sample of healthy schoolchildren, both maternal smoking as well as neonatal oxygen score were weakly associated with the symptom at 7 years. The overall findings suggest that a family history of asthma does not significantly increase the risk of wheeze in the long term low birthweight survivors.

The association between neonatal oxygen score and childhood cough was not uniform in the cohort. The excess of cough was especially pronounced in the very low birthweight children who received neonatal intensive care (figure). This contrasts with the very low prevalence of symptoms in the other very low birthweight children who did not receive neonatal respiratory treatment. It is probable that very low birthweight children were more vulnerable to the effect of neonatal respiratory treatment than the remainder of the cohort and that the symptom that they manifested at the age of 7 was cough rather than wheeze. The hypothetical association between the symptoms at 7 years and the level of neonatal respiratory treatment (oxygen score) was confirmed by multiple logistic regression analysis, allowing for other variables which could have influenced the occurrence of symptoms.

Although the association between childhood symptoms and oxygen score confirmed that the former could be attributable to the level of neonatal intensive care received, it does not prove that the association is causal. It remains possible that their association was linked by other confounding factors such as host vulnerability, leading to both an increase in the level of neonatal respiratory treatment required as well as long term respiratory symptomatology. The relatively low level of symptoms, especially wheeze, in the low birthweight children compared with the reference group argues against the association being the result of preferential recall bias by their parents. But it also implies that even if the association were causal, the scope for improvement in symptoms in long term survivors might be limited. Similarly, though neonatal lung injury is clearly associated with mechanical ventilation,[36] there was no significant excess of symptoms in those who received this form of treatment compared with those who had oxygen treatment alone. Although this is a welcome finding, it does suggest that the potential for improving long term symptomatology through continuing advances in neonatal ventilatory technology is not great. Among all the perinatal risk factors examined, maternal smoking was the only significant factor that might be amenable to manipulation. With evidence that the effect of maternal smoking could be due to both antenatal and well as postnatal exposure, it would be important to advise abstention early in pregnancy or before conception.

In conclusion, we have found a relatively small excess of coughing in 7 year old children of low birthweight compared with a random sample of healthy schoolchildren of the same age. This symptom has been overlooked by previous studies. Its significance in the low birthweight cohort was confirmed by its association with the level of neonatal respiratory treatment. With progressive reduction in the level of symptoms experienced by the low birthweight cohort over the previous few years, one can afford to be optimistic about the long term outlook. This speculation could only be confirmed by longitudinal studies in subsequent years.

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References

[1] Outerbridge EW, Nogrady MB, Beaudry PH, *et al.* Idiopathic respiratory distress syndrome. *Am J Dis Child* 1972;**123**:99–104.

[2] Bryan MH, Hardie MJ, Reilly BJ, *et al.* Pulmonary function studies during the first year of life in infants recovering from the respiratory distress syndrome. *Pediatrics* 1973;**52**:169–78.

[3] Johnson JD, Malachowski NC, Grobstein R. Prognosis of children surviving with the aid of mechanical ventilation in the newborn period. *J Pediatr* 1974;**84**:272–6.

[4] Stocks J, Godfrey S, Reynolds EOR. Airway resistance in infants after various treatments for hyaline membrane disease: special emphasis on prolonged high levels of inspired oxygen. *Pediatrics* 1978;**61**:178–83.

[5] Fitzhardinge PM. Follow-up studies in infants treated by mechanical ventilation. *Clin Perinatol* 1978;**5**:451–61.

[6] Lindroth M, Jonson B, Svenningsen NW, *et al.* Pulmonary mechanics, chest X-ray and lung disease after mechanical ventilation in low birth weight infants. *Acta Paediatr Scand* 1980;**69**:761–70.

[7] Wong YC, Beardsmore CS, Silverman M. Pulmonary sequelae of neonatal respiratory distress in very low birthweight infants: a clinical and a physiological study. *Arch Dis Child* 1982;**57**: 418–24.

[8] Myers MG, McGuinness GA, Lachenbruch PA. Respiratory illnesses in survivors of infants respiratory distress syndrome. *Am Rev Respir Dis* 1986;**133**:1011–8.

[9] Gerhardt T, Hehre D, Feller R, *et al.* Serial determination of pulmonary function in infants with chronic lung disease. *J Pediatr* 1987;**110**:448–56.

[10] Lamarre A, Linsao L, Reilly BJ, *et al.* Residual pulmonary abnormalities in survivors of idiopathic respiratory distress syndrome. *Am Rev Respir Dis* 1973;**108**:56–61.

[11] Heldt GP, McIlroy MB, Hansen TN, *et al.* Exercise performance of the survivors of hyaline membrane disease. *J Pediatr* 1980;**96**:995–9.

[12] Stahlman M, Hedvall G, Lindstrom D, *et al.* Role of hyaline membrane disease in production of later childhood lung abnormalities. *Pediatrics* 1982;**69**:572–6.

[13] Borkenstein J, Borkenstein M, Rosegger H. Pulmonary function studies in long-term survivors with artificial ventilation in the neonatal period. *Acta Paediatr Scand* 1980;**69**:159–63.

[14] Mansell AL, Driscoll JM, James LS. Pulmonary follow-up of moderately low birthweight infants with and without respiratory distress syndrome. *J Pediatr* 1987;**110**:111–5.

[15] Riedel F. Long term effects of artificial ventilation in neonates. *Acta Paediatr Scand* 1987;**76**:24–9.

[16] Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Aber VR, Silverman M. Airway responsiveness in low birthweight children and their mothers. *Arch Dis Child* 1988;**63**:905–10.

[17] du V Florey C, Leeder SR. *Methods of cohort studies of chronic airflow limitation.* Geneva: WHO Regional Publications, 1982.

[18] Baker RJ. *The GLIM system: release 3.* London: Royal Statistical Society, 1978.

[19] Johnston IDA, Bland TM, Anderson HR. Ethnic variation in respiratory morbidity and lung function in childhood. *Thorax* 1987;**42**:542–8.

[20] Hedges BM. Question wording effects: presenting one or both sides of a case. *The Statistician* 1978;**28**:83–99.

[21] Paradise JL, Bluestone CD, Bachman RZ, *et al.* History of recurrent sore throat as an indication for tonsillectomy. *N Engl J Med* 1978;**298**:409–13.

[22] Watkins CJ, Burton P, Leeder S, *et al.* Doctor diagnosis and maternal recall of lower respiratory illness. *Int J Epidemiol* 1982;**11**:62–6.

[23] Archer LNJ, Simpson H. Night cough counts and diary card scores in asthma. *Arch Dis Child* 1985;**60**:473–5.

[24] Salome CM, Peat JK, Britton WJ, *et al.* Bronchial hyperresponsiveness in two populations of Australian school children. Relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;**11**:271–8.

[25] Bryan MH, Levison H, Swyer PR. Pulmonary function in infants and children following acute neonatal respiratory distress syndrome. *Bull Physiopath Respir* 1973;**9**:1587–600.

[26] Dinwiddie R, Mellor DH, Donaldson SH, *et al.* Quality of survival after artificial ventilation of the newborn. *Arch Dis Child* 1974;**49**:703–10.

[27] Stahlman M, Hedvall G, Dolanski E, *et al.* A six-year follow-up of clinical hyaline membrane disease. *Pediatr Clin North Am* 1973;**20**:433–46.

[28] Kamper J. Long term prognosis of infants with severe idiopathic respiratory distress syndrome II. Cardiopulmonary outcome. *Acta Paediatr Scand* 1978;**67**:71–6.

[29] Weiss ST, Tager IB, Speizer FE, *et al.* Persistent wheeze: its relation to respiratory illness, cigarette smoking and level of pulmonary function in a population sample of children. *Am Rev Respir Dis* 1980;**122**:697–707.

[30] Colley JRT, Holland WW, Corkhill RT. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet* 1974;**ii**:1031–4.

[31] Yarnell JWG, St Leger AS. Respiratory illness, maternal smoking habit and lung function in children. *Br J Dis Chest* 1979;**73**:230–6.

[32] Hasselblad V, Humble CG, Graham MG, *et al.* Indoor

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Pressure flow characteristics of the valve in spacer devices

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SUMMARY The valve system in the mouth piece of two spacer devices was analysed. Pressures required to open and close the non-rebreathing valve were very low (<0·1 kPa). Inspiratory flow requirements were within physiological limits for infants' normal tidal breathing. Expiratory flow requirements varied significantly, and the flow required to prevent rebreathing from the chamber may exceed the physiological flow limits for normal tidal breathing.

Recurrent wheezing attacks in children aged less than 18 months are common but difficult to treat.[1] The use of conventionally nebulised medication is not commonly recommended in this age group because of inefficacy of bronchodilators. Oral bronchodilators have more side effects than inhaled β_2 agonists and are frequently not helpful. Clinical experience, however, shows that, even in early infancy, improvement of broncho-obstructive symptoms can be achieved in some infants by treating them with inhaled bronchodilators. Wet nebulisers can be used to deliver bronchodilators but are time consuming and expensive. A simpler and cheaper device would allow inhaled bronchodilators to be used more widely, particularly at home.

Aerosol holding chambers (spacer devices) have recently been introduced to assist aerosol delivery in children too young to use metered dose aerosol successfully. These devices have been shown to decrease oropharyngeal deposition and increase deposition in the lungs, so long as they have an appropriate design.[2] Two commercially available spacers appear to fulfil the design requirements. These are the Volumatic and the Nebuhaler.

The use of spacer devices has been advocated in infants by attaching a face mask to the mouth piece.[3] However, no information is available on the pressure and flow that are required to operate the non-rebreathing valves. The present study was performed to define pressure and flow characteristics of the valve system and their inter-relationship with the orientation of the airspacer. This knowledge is necessary before we try to define the place of spacer devices in the treatment of small and sick infants who might be unable to generate the necessary flow and pressure to operate the valve system. Failure to open the valve during inspiration would result in failure to deliver the bronchodilator, while failure to close the valve during expiration would leave the infant vulnerable to rebreathing from the spacer.

Methods

The valve system in the mouth piece of the commercially available spacer devices Nebuhaler (Astra) and Volumatic (Glaxo) were analysed. Five examples of each model were tested. Simulated 'inspiration' and 'expiration' through the mouth piece was performed by slowly increasing air flow until the valve opened or closed, respectively. Pressure inside the spacer was measured to determine precisely when the valve closed or opened. The time of valve closure or opening was obtained when the spacer pressure changed abruptly. The pressure on the mouth side of the valve and flow across the valve (Fleisch No 1 pneumotachograph) were recorded at that time. The position of the spacer recommended for use in adults is horizontal. It seemed more likely that the spacers would be given to infants lying supine (spacer vertical) or propped up in their parent's arms (spacer at an angle of about 45°).

We therefore recorded mouth pressure and flow with the spacer held in three different orientations: horizontal, at an angle of 45°, and vertical. The mouth piece end of the device was raised (45°, vertical) during inspiration and declined (45°, vertical) during expiration in order to measure the opening and closing pressure respectively. For each of the 10 spacers the measurements were repeated five times in a random order in each position. The intradevice and interdevice coefficients of variation for the obtained values were calculated for both spacers. In addition, the effect of activating a metered dose inhaler on the spacer valve was tested by repeating the measurements in one position (inspiration, 45° vertical) after 10, 20, and 100 activations, respectively. Student's independent *t* test was used to compare sample means.

Table 1 *Mean (SD) inspiratory and expiratory flow rates in ml/second*

	Inspiration			*Expiration*		
	Vertical	*45°*	*Horizontal*	*Vertical*	*45°*	*Horizontal*
Nebuhaler (n=5)	12·0 (1·3)	11·9 (1·7)	9·9 (1·3)	73·9 (2·5)	71·3 (5·2)	38·1 (6·3)
Volumatic (n=5)	10·3 (0·6)	9·7 (1·0)	7·0 (1·0)	24·3 (4·0)	20·7 (3·5)	16·0 (5·0)

*All differences between space devices were significant ($p<0\cdot0001$).

Table 2 *Coefficients of variation for inspiratory and expiratory flow rates (%)*

	Inspiration			*Expiration*		
	Vertical	*45°*	*Horizontal*	*Vertical*	*45°*	*Horizontal*
Nebuhaler (n=5)						
Intradevice						
Median	9	13	8	3	4	11
Range	5–17	6–18	8–13	1–5	3–9	6–19
Interdevice	11	14	13	3	7	16
Volumatic (n=5)						
Intradevice						
Median	4	10	7	6	6	24
Range	1–6	5–12	4–22	4–22	3–29	15–49
Interdevice	6	11	14	17	17	31

Results

In each position the expiratory flows required to close the valve were higher than the inspiratory flows required to open the valve (*t* test, $p<0\cdot0001$) and were greater with the Nebuhaler in all positions than with the Volumatic (*t* test, $p<0\cdot0001$) (table 1). The pressures required to open and close the spacer valves were always less than 0·1 kPa (negative or positive) in all positions.

The intradevice coefficients of variation for the two airspacers did not differ significantly (*t* test, $p>0\cdot05$) (table 2). The interdevice coefficients of variation were similar for Volumatic and Nebuhaler except during expiration when the coefficients for Volumatic were more variable.

The use of a metered dose inhaler did not effect the valve function of either spacer. The flows and pressures required to open the valves following 10, 20, or 100 activations of the inhaler were not significantly greater than those required to open the valve under control conditions.

Discussion

Spacer devices potentially represent a significant advance in the treatment of asthma as they allow inhaled β_2 agonists to be given to younger children who are unable to use a metered dose aerosol successfully. However, before these devices are widely adopted, their physical characteristics need to be evaluated. The results of the present study have shown that the pressures needed to open and close the valve in both airspacers are minimal (<0·1 kPa). These pressures should easily be generated even by small or sick infants.

The inspiratory flows required to open the spacer valves were very low (range 7–12 ml/second) regardless of the position of the spacer even with the spacer vertical (valve uppermost). These values of inspiratory flow can easily be achieved by infants. Reported values for peak inspiratory flow during tidal breathing in infancy range between 80–150 ml/second.[4–6] In addition, inspection of flow-volume loops in both healthy infants and those with bronchial obstruction show that during most of normal tidal inspiration the flow is sufficient to open the valve. Before the use of spacers becomes widespread in infants with bronchial obstruction, some assessment of whether such infants can generate sufficient pressure and flow to operate the valve is needed.

During expiration the flows required to close the Volumatic valve were slightly higher than those required to open the valve, but lie still in a range easily achievable by infants. The flows required to close the Nebuhaler valve were significantly higher than those required to close the Volumatic valve. In the vertical position the expiratory flows averaged 73·9 ml/second (range 69·8–81·5 ml/second) for the Nebuhaler and 24·3 ml/second (range 11·7–31·2 ml/second) for the Volumatic. These flows required for valve closure in Nebuhaler may not be achievable by infants. The reported values for peak tidal expiratory flow in normal infants (5 to 11 months of age) are 70 ml/second.[5] During most of expiration the flow is likely to be considerably less, especially in infants with obstructive airway diseases. Infants with expiratory flow limitation during tidal breathing can not increase expiratory flows without increasing lung volume. Failure to close the spacer valve exposes the infant to the risk of rebreathing.

The intradevice and interdevice coefficients of variation for both types of spacer devices are acceptable. The higher coefficients of variation found during expiration in the Volumatic spacer device than found for Nebuhaler are interesting but of no clinical importance. Thus the intradevice or interdevice variability is not an additional factor to be considered when using airspacers in infancy.

Although up to 100 activations of a metered dose inhaler did not result in an increase in the pressure or flow required to open the spacer valve, prolonged use without adequate cleaning could result in the valve becoming 'sticky', thus requiring greater pressures and flows to operate the valve. Furthermore, the simulated inspiration and expiration in the present study were performed using room air. It is possible that humid expired air could cause the valve to become 'sticky'.

In conclusion, our results show that the flows required to open the valves in the Volumatic and Nebuhaler spacer devices are within the range of reported values that can be achieved even by flow obstructed infants. Flows required to close the valve, however, may not lie within reported physiological limits for normal tidal breathing of even healthy infants. Further studies, with particular reference to the flows generated during tidal breathing, and the orientation of the device, are needed to evaluate the possible role of aerosol holding chambers in the treatment of wheezy infants.

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References

[1] Silverman M. Bronchodilators for wheezy infants? *Arch Dis Child* 1984;**59**:84–7.

[2] Kim CS, Eldridge MA, Sackner MA. Oropharyngeal deposition and delivery aspects of metered-dose inhaler aerosols. *Am Rev Respir Dis* 1987;**135**:157–64.

[3] Murray M, O'Callaghan C. How to treat the wheezy infant. *Maternal and Child Health* 1988;Feb:47–54.

[4] Doershuk CF, Downs TD, Matthews LW, Lough MD. A method for ventilatory measurements in subjects 1 month–5 years of age: normal results and observations in disease. *Pediatr Res* 1970;**4**:165–74.

[5] Lindroth M, Johnson B, Ahlstrom H, Svenningsen W. Pulmonary mechanics in early infancy, Subclinical grunting in low-birth-weight infants. *Pediatr Res* 1981;**15**:979–84.

[6] Milner AD, Saunders RA, Hopkin IE. Tidal pressure/volume and flow/volume respiratory loop patterns in human neonates. *Clinical Science and Molecular Medicine* 1978;**54**:257–64.

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Polycystic ovary syndrome in a virilised, premenarcheal girl

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SUMMARY A premenarcheal girl aged 12 years presented with an abdominopelvic mass and virilisation. A large ovarian cyst was removed at laparotomy. A histological diagnosis of polycystic ovarian syndrome was made, with no evidence of an associated masculinising tumour.

Polycystic ovary disease was initially described by Stein and Leventhal in 1935 as comprising the triad of obesity, hirsutism, and amenorrhoea in women with bilaterally enlarged polycystic ovaries.[1] In more recent years the term 'polycystic ovary syndrome' has come to be applied to a broad range of clinical features including hirsutism, secondary amenorrhoea or other menstrual irregularities, infertility, obesity, and enlarged ovaries. Frank virilisation is rare and the syndrome is usually seen in the third or fourth decades of life, but there are isolated reports of it in premenarcheal girls. This report describes a 12 year old girl with pronounced virilisation, a large ovarian cyst, and polycystic changes in both ovaries.

Case report

A girl presented at the age of 12 years and 5 months with several months history of persistent abdominal swelling. She was otherwise asymptomatic and she was premenarcheal.

On examination her height and weight were on the 75th centile for chronological age, and she had normal blood pressure. She had signs of virilisation, namely mild hirsutism, a deep voice, acne, and an enlarged clitoris. A large firm mass arising from her pelvis and extending to the level of her umbilicus was palpable. Her breast development was Tanner stage 2 and pubic hair stage 3.

Investigations showed that she had a normal female karyotype. Bone age was advanced at 15 years; skull radiographs were normal. Her endocrinological investigations are summarised in the table. The plasma testosterone concentration was considerably raised, and the androstenedione concentration was also raised. The other measurements were within normal limits for her pubertal stage. A large right sided ovarian cyst was shown on ultrasonography.

At laparotomy a large cyst, about 15 cm in diameter was found arising from the right ovary. The left ovary was slightly enlarged but otherwise normal. A right salpingo-oophorectomy and a wedge resection of the left ovary were carried out.

On histological examination by two independent pathologists no evidence of an androgen secreting tumour was found, and both ovaries had a polycystic appearance.

Immediately after operation the plasma testosterone concentration fell to 2·6 nmol/l, but then rose again over the next few months. High dose dexamethasone failed to suppress androgen concentrations. Buserelin, a synthetic analogue of luteinising hormone releasing hormone, was given intranasally for three weeks and this resulted in a suppression of her plasma androgen concentration, which was sustained for some months. Her plasma testosterone concentration subsequently rose again, however, to 5·7 nmol/l and a further ultrasound scan showed polycystic changes in her remaining ovary. In view of these findings and her lack of breast development she was given a low dose combined oral contraceptive containing ethinyloestradiol 30 µg and desogestrol 150 µg (Marvelon, Organon). Six months later her plasma testosterone concentration had fallen to <0·7 mmol/l, and neither luteinising hormone nor follicle stimulating hormone were detectable in the serum.

Table *Summary of endocrinological investigations*

	Patient's value	*Normal range*
Testosterone (nmol/l)	9·3	0·9–2·7
Androstenedione (nmol/l)	5·0	0·9–3·9
Luteinising hormone (IU/l)	9·0	5·6–13·6
Follicle stimulating hormone (IU/l)	6·0	2·4–7·7
Oestradiol (nmol/l)	0·21	0·03–0·22
17–OH progesterone (nmol/l)	2·0	0·4–4·2

Discussion

This patient had isolated polycystic ovary syndrome presenting with a pelvic mass and clinical signs of virilisation. An adrenal source of androgen excess was excluded by the failure of high dose dexamethasone to suppress plasma testosterone, and no ovarian tumour was found on histological examination. There was a temporary suppression of androgen concentrations while the patient was taking intranasal Buserelin: gonadotrophin releasing hormone agonists can suppress gonadotrophin secretion in patients with polycystic ovary syndrome.[2]

There are three unusual features about this case. Firstly, the degree of virilisation was greater than expected for a patient with polycystic ovary syndrome: the considerably raised concentrations of testosterone in this patient were more suggestive of an adrenal or ovarian tumour, but these were excluded.

The second unusual feature was the early age of onset of the disease and its timing in relation to puberty. Such a presentation at this age would again make an adrenal lesion or an ovarian neoplasm most likely. There are a few isolated reports of polycystic ovary syndrome occurring in premenarcheal girls without an associated ovarian tumour. Prunty *et al*, described a girl of 17 years who presented with primary amenorrhoea and severe virilisation.[3] In 1972 Richmond *et al* reported a girl who presented at the age of 13 years and 2 months for investigation of hirsutism.[4] She was premenarcheal with virilisation and acanthosis nigricans. Wedge biopsy specimens of both ovaries showed histological changes consistent with polycystic ovary syndrome but with no associated tumour. In this case the maximum plasma testosterone concentration on initial investigation was 4·9 nmol/l. Ovulation and regular menstruation were induced by treatment with clomiphene.

More recently, Rao *et al* reported a 12 year old girl with progressive hirsutism of nine months' duration.[5] This patient was also premenarcheal with clinical signs of virilisation. Her plasma testosterone concentrations were initially measured on three occasions as being between 4·8 and 9·3 nmol/l. Both ovaries were enlarged on exploratory laparotomy, and bilateral wedge resections of the ovaries were carried out, which showed histological evidence of polycystic ovary syndrome but no tumour. In this patient the testosterone concentrations did not fall after operation, and she was treated successfully with an oral contraceptive.

Thirdly, polycystic ovary syndrome is usually characterised by some enlargement of the ovaries, but is rarely associated with large cysts. The patients in the reports above all had bilaterally moderately enlarged ovaries, but none had individual cysts of the size seen in our patient. This feature also suggests the possibility of associated malignancy, which was not found.

The pathophysiology of polycystic ovary syndrome is still not clearly understood. There are three main approaches to its treatment. Ovulation may be induced by various drugs including clomiphene citrate, human chorionic gonadotrophin, and pure follicle stimulating hormone; the older therapeutic approach of ovarian wedge resection is used much less often today. Antiandrogenic drugs such as cyproterone acetate may be used to reverse the clinical features of masculinisation. Low dose oral contraceptives suppress gonadotrophin secretion and reduce ovarian secretion of androgen; they also reduce the adrenal production of steroids. In this patient an oral contraceptive successfully suppressed both testosterone and gonadotrophin concentrations.

In conclusion, this case and a few previously reported show that isolated polycystic ovary syndrome can be found in virilised premenarcheal girls. In such patients, however, an adrenal source of excess androgen or a virilising tumour of the ovary must be excluded.

References

1. Stein IF, Leventhal ML. Amenorrhoea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1935;**29**:181–91.
2. Chang RJ, Laufer LR, Meldrum DR, *et al.* Steroid secretion in polycystic ovarian disease after ovarian suppression by a long-acting gonadotrophin-releasing hormone agonist. *J Clin Endocrinol and Metab* 1983;**56**:897–903.
3. Prunty FTG, Brooks RV, Dupre J, *et al.* Virilisation and the human ovary: including observations on the Stein-Leventhal syndrome. *Proceedings of the Royal Society of Medicine* 1964; **57**:529–32.
4. Richmond SS, Goldstein DP, Dluhy RG, *et al.* A 13 year old premenarchal female with the Stein-Leventhal syndrome. *Fertil Steril* 1972;**23**:508–12.
5. Rao JK, Chihal HJ, Johnson CM. Primary polycystic ovary syndrome in a premenarchal girl: a case report. *J Reprod Med* 1985; **30**:361–5.

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Successful treatment of a harlequin fetus

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SUMMARY We report the prolonged survival of a harlequin fetus who was treated with intensive supportive measures, emollients, and oral etretinate.

The Harlequin fetus is the severest of the congenital ichthyoses and is usually considered to be fatal.

Case report

A baby girl, who weighed 2360 g, was delivered at 38 weeks' gestation after a normal pregnancy. There was no relevant family history.

Her skin consisted of thick, yellow, leathery plaques separated by deep red cracks. There was ectropion of the eyelids and eclabion of the mouth. The ears were flattened and bound to the side of the head. The digits of the hands and feet were flexed and bound together by tight membranes. Examination of a skin biopsy by light and electron microscopy showed changes consistent with the clinical diagnosis of a harlequin fetus.

The baby was nursed in an humidified incubator and fluids were administered via an umbilical artery catheter. Fluids were progressively increased to a maximum of 250 ml/kg per day in order to maintain a normal serum urea. A mixture of equal parts of white soft paraffin and liquid paraffin containing 1% salicylic acid was applied to the skin every three hours. She was bathed twice daily. Emulsifying ointment and antiseptic solution were added to the water.

After 24 hours she became tachypnoeic and feverish. Arterial blood gases showed pH 7·45, $PaCO_2$ 3·01 kPa, PaO_2 7·1 kPa, bicarbonate 15·7 mmol/l, and base excess 7·1. The serum salicylate concentration was 586 mg/l. The salicylate containing emulsion was discontinued and topical treatment was continued with simple white soft paraffin and liquid paraffin.

On the third day oral etretinate, 1 mg three times daily, was commenced. Initially an unstable solution was prepared each day by the hospital pharmacy but later a dry diluent was obtained (Avicel 101, Honeywell and Stain Ltd, Wallington) enabling the production of a stable powder suitable for outpatient use.

Her skin gradually softened and the hard yellow plaques separated, leaving a red scaly surface beneath. The perioral skin became more mobile and by the fifth day she was able to breast feed. Tight bands of skin around the wrists and ankles responded to topical 10% urea in liquid paraffin applied under an occlusive dressing. Plugs of keratin in the external auditory canals cleared with Cerumol (LAB) ear drops. At two weeks of age the skin was greatly improved and she was able to maintain her body temperature in an open cot. She went home on day 23. Continuing treatment consisted of twice daily baths, topical paraffin emulsion, chloramphenicol and hypromellose eye drops, and oral etretinate.

As the skin improved the frequency of bathing and topical treatment was reduced. The dose of etretinate was halved at 10 months and discontinued at one year. No abnormalities of liver function or renal function were detected during etretinate treatment.

Weight gain was initially poor but subsequently improved, however at 21 months her weight and height were still below the third centile and the head circumference was on the fifth centile. Her developmental progress was within normal limits. The skin was dry, erythematous, and covered in large, thin scales. Ectropion and eclabion had resolved and the membranes binding the digits had disappeared.

Discussion

The appearance of the harlequin fetus is bizarre and may be abhorent to both parents and professionals. Paediatric textbooks offer an appalling prognosis with death occurring within a few days or weeks.[1] Paediatricians may therefore choose not to pursue active management.

The skin is thick, inelastic, and permeable. Death is believed to result from excessive fluid loss, inability to feed because of eclabion, and respiratory embarrassment caused by limitation of chest movement.[2] In order to minimise evaporative water losses our patient was nursed in a humidified incubator and treated topically with paraffin emulsion. The addition of salicylic acid to the emulsion resulted in salicylate toxicity and had to be withdrawn. Despite these measures it was still necessary to provide large volumes of parenteral fluids to maintain normal urea and electrolyte values.

Lawlor and Peiris first used etretinate to treat a harlequin fetus in 1985.[3] Etretinate is a synthetic retinoid derived from Vitamin A. Its mode of action is unknown but retinoids have been shown to control differentiation and proliferation of keratinising and non-keratinising epithelia. The main systemic side effects are teratogenicity and the development of exostoses with prolonged use.[4] Dose dependent changes in liver function tests (bilirubin, alkaline phosphatase, and transaminases) have been reported in adults. However, both our patient and that of Lawlor and Peiris had normal values.

The long term outcome of the harlequin fetus is unknown, our case being only the second baby to have survived beyond the first birthday. Lawlor and Pieris published further details of their case when she was 10 months old.[5] The skin was then dry, erythematous, and ichthyotic. Previously the longest surviving case had been that of Buxman *et al* who lived until 9 months when he suddenly died.[6] He had received emollients and supportive care only.

The death of a harlequin fetus is not inevitable. Aggressive supportive care is probably the single most important part of management. Oral etretinate may be of additional benefit but current experience is very limited.

References

[1] Esterly NB, Solomon LM. Congenital and hereditary disorders of the skin. In: Avery ME, Taeusch HW, eds. *Schaffer's diseases of the newborn.* Philadelphia: W B Saunders, 1984:868.

[2] Kouskoukis C, Minas A, Tousimis D. Ichthyosis congenital fetalis (harlequin fetus). *Int J Dermatol* 1982;**21**:347–8.

[3] Lawlor F, Peiris S. Harlequin fetus successfully treated with etretinate. *Br J Dermatol* 1985;**112**:585–90.

[4] Glover MT, Peters AM, Atherton DJ. Surveillance for skeletal toxicity of children treated with etretinate. *Br J Dermatol* 1987;**116**:609–14.

[5] Lawlor F, Peiris S. Progress of a harlequin fetus treated with etretinate. *J R Soc Med* 1985;**78**:(suppl 11):19–20.

[6] Buxman MM, Goodkin PE, Fahrenbach WH, Dimond RL. Harlequin ichthyosis with epidermal lipid abnormality. *Arch Dermatol* 1979;**115**:189–93.

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Effect of dystonic movements on oesophageal peristalsis in Sandifer's syndrome

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SUMMARY A 5 year old girl with gross gastro-oesophageal reflux had pronounced dystonic neck movements that resolved after fundoplication and resolution of the oesophagitis (Sandifer's syndrome). Oesophageal manometry before operation showed that peristalsis improved when she tilted her head to one side. Dystonic posturing may promote acid clearance from the distal oesophagus.

Case report

A 5 year old girl was referred with a 12 week history of belching and vomiting, mainly after food. A barium swallow examination was reported to show the presence of a hiatus hernia. Her appetite had decreased appreciably, and she was thought to have lost weight. She vomited about three times a day; occasionally altered blood was present in the vomit. Her general health had been good, although she had an operation for squint, had had grommets inserted, and had a history of urinary tract infections. On physical examination she looked well though pale, and was on the 50th centile for both height and weight. The most striking feature was pronounced neck dystonia with repeated rotation of the neck and tilting of the head towards the left shoulder (fig 1), sometimes associated with bending the upper part of her body to the left. No other abnormalities were found on neurological examination, and the dystonic movements stopped when she was asleep.

INVESTIGATIONS

Her haemoglobin concentration was 91 g/l with a microcytic film, and the platelet count was raised at 680×10^9/l, suggesting chronic blood loss. Microscopy of her sputum showed fat laden macrophages consistent with recurrent aspiration, and 24 hour oesophageal pH monitoring confirmed severe gastro-oesophageal reflux, with a reflux index (percentage of time the pH was less than 4 in the lower oesophagus) of 39% (normal <4%). A severe ulcerative oesophagitis of the lower half of the oesophagus was found at endoscopy and confirmed by histological examination of biopsy specimens. No hiatus hernia was seen. Oesophageal manometric recordings during 5 ml swallows of water showed low amplitude, slowly propagated, peristaltic waves in the middle and lower oesophagus (fig 2(a)) with a mean amplitude of 47 and 25 mm Hg, respectively. These increased to means of 74 and 52 mm Hg when the patient simulated her dystonic neck posture (fig 2(b)). The mean speed of propagation of peristaltic swallows was 2·5 cm/s with the head in the midline, and 4·0 cm/s while the head was rotated and tilted towards the left shoulder.

PROGRESS

She was started on sucralfate 500 mg, cisapride 3 mg, and ranitidine 15 mg, all taken four times a day. Over the next six weeks, however, she continued to vomit and make dystonic neck movements. Repeat endoscopy showed that the severe ulcerative oesophagitis was unchanged, and a Nissen fundoplication was therefore carried out. Three months after operation all her symptoms—including the abnormal posturing—had completely resolved. Further oesophageal manometry was considered ethically unjustifiable.

Discussion

The association between abnormal movements and gastro-oesophageal reflux with hiatus hernia was first recognised by Sandifer,[1] and the association of abnormal posturing and oesophagitis without hiatus hernia has also been described.[2] Characteristic

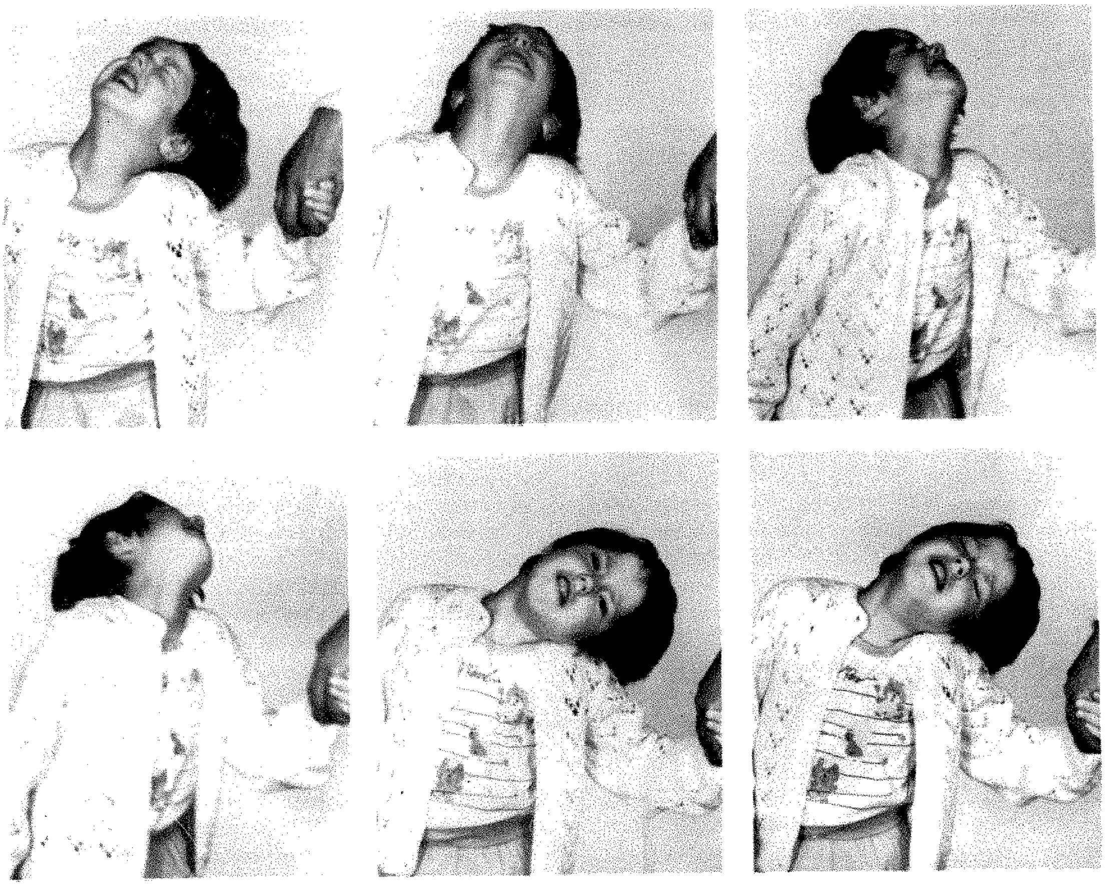
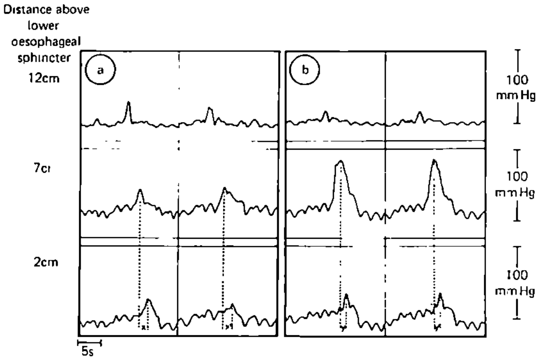


Fig 1 *Dystonic neck movements associated with severe gastro-oesophageal reflux.*

movements include extension and rotation of the neck. Some children allow their heads to hang in extension over the edge of the bed while lying supine. Dystonia does not occur during sleep, and once the gastro-oesophageal reflux has been treated effectively (either medically[3] or surgically[1]) the abnormal movements cease. Children may initially be referred to one of a number of different specialists, including ophthalmologists,[4] neurologists,[1 3] or psychiatrists,[3] and underlying gastro-oesophageal reflux should be considered in all patients who present with dystonic neck movements and abnormal posturing. Most children with gastro-oesophageal reflux, however, do not develop abnormal posture[5] and the connection between reflux and dystonia has been a matter for speculation. It has been suggested that the movements in some way bring about symptomatic relief but the precise mechanism has not been elucidated.[1 5]

As far as we are aware, manometric studies have not previously been reported in a case of Sandifer's syndrome. In our patient the low amplitude and slow propagation of oesophageal peristalsis may have reflected a primary motility defect or been secondary to the oesophagitis.[6] We were able to show that the dystonic posturing produced an increase in the velocity and amplitude of the peristaltic waves in the oesophagus, and we postulate that this would promote the clearance of acid from the lower oesophagus and thereby relieve the symptoms. We have not been able to reproduce these findings in three normal adult controls or in two children with oesophageal reflux but no dystonia, and the association between posture and



Simultaneous recordings from three sites in the oesophagus using a perfused manometry catheter

Fig 2 *Three channel oesophageal manometry showing an increase in amplitude and velocity of peristalsis when head rotated and tilted towards the left shoulder. (a) Shows two representative swallows with 5 ml boluses while head in the midline. Peristaltic waves are broad based and of low amplitude. (b) Shows two representative swallows with 5 ml boluses while head rotated to the left. Amplitude of peristaltic waves is increased especially in middle channel. Distances y and y' are less than x and x' showing that peristaltic waves are travelling more rapidly in mid to lower oesophagus.*

oesophageal motility remains unclear. Manometric studies in future patients may help to explain the abnormal movements seen in this rare and intriguing disorder.

References

[1] Kinsbourne M. Hiatus hernia with contortions of the neck. *Lancet* 1964;**i**:1058–61.

[2] Ramenofsky ML, Buyse M, Goldberg MJ, Leape LL. Gastroesophageal reflux and torticollis. *Journal of Bone and Joint Surgery* 1978;**60**:1140–1.

[3] Bray PF, Herbst JJ, Johnson DG, Book LS, Ziter FA, Condon VR. Childhood gastroesophageal reflux. Neurologic and psychiatric syndromes mimicked. *JAMA* 1977;**237**:1342–5.

[4] O'Donnell JJ, Howard RO. Torticollis associated with hiatus hernia. *Am J Ophthalmol* 1971;**71**:1134–7.

[5] Sutcliffe J. Torsion spasms and abnormal postures in children with hiatus hernia Sandifer's syndrome. In: HJ Kaufman, ed. *Progress in pediatric radiology.* Vol 2. Chicago: Karger, 1969: 190–7.

[6] Cucchiara S, Staiano A, Di Lorenzo D, *et al.* Esophageal motor abnormalities in children with gastroesophageal reflux and peptic oesophagitis. *J Pediatr* 1986;**108**:907–10.

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Obesity and diabetic control

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SUMMARY Children with diabetes mellitus are not significantly heavier than their peers, and those who are obese do not have poorer diabetic control.

Adults with insulin dependent diabetes are often obese, and this may adversely affect their diabetic control, resulting in complications.[1] We are unaware of any publication on the incidence of obesity in childhood diabetes or of its effect on diabetic control. In this study we report the incidence of obesity in children attending our diabetic clinic, and relate this to their diabetic control.

Patients and methods

One hundred and six children (58 boys and 48 girls) attending the diabetic clinic at the Bristol Children's Hospital who had had diabetes for more than one year were studied over the 12 month period. Their mean age during the study period was 14·9 years (range 5–22), and their mean age at diagnosis was 8·3 years (range 1·3–15·9). The mean duration of their diabetes was 6·4 years (range 1–16·6). All the children were receiving quick and intermediate acting insulins twice daily, with the exception of three patients who used an insulin pump.

They were seen at intervals of three months, when their height and weight (measured with a Harpenden stadiometer) were recorded. Skinfold thickness (triceps and subscapular) was measured using a Harpenden skinfold caliper, and puberty was assessed clinically by the method of Tanner and Whitehouse.[2] Each child's height, weight, and skinfold thickness was then taken as the average over visits during the year of investigation.

The children were regarded as overweight when

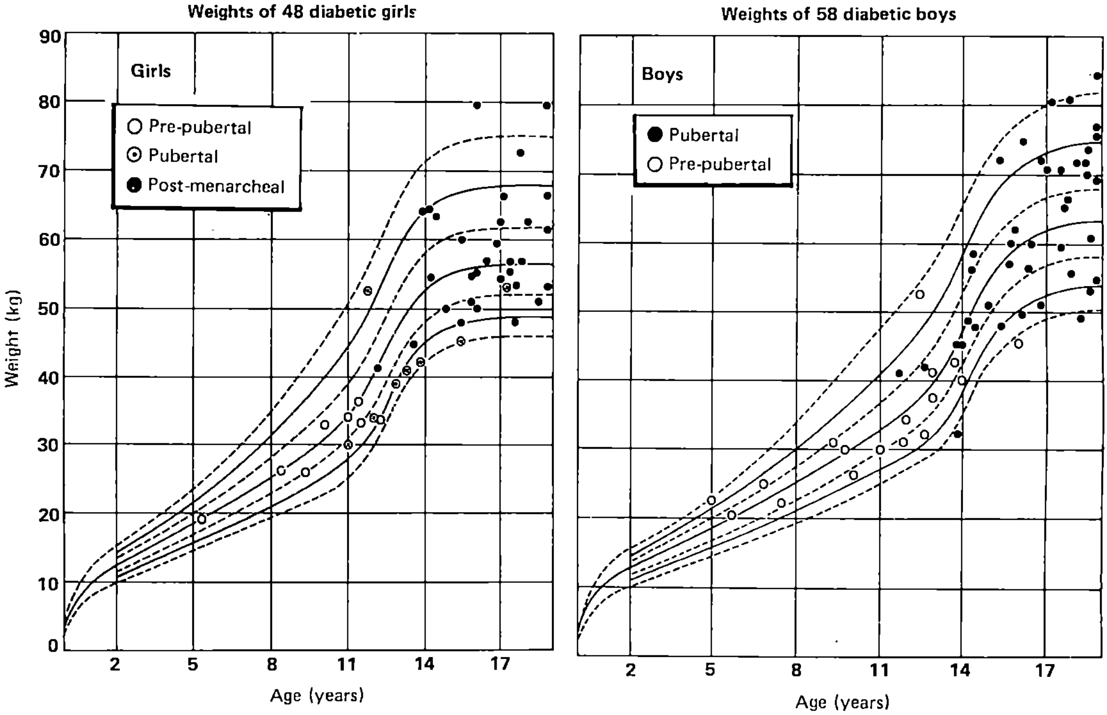

Figure *Weights in diabetic girls and boys.*

their absolute weight was more than 20% above the median for their age and sex (Tanner charts), or their relative standard weight percentile (actual weight/standard weight×100) was greater than 120%, or their skinfold thickness, both triceps and subscapular, was above the 70th centile (Tanner charts).

Glycated haemoglobin (HbA_{1c}) was measured at each visit by electroendosomosis. The mean annual HbA_{1c} value was calculated and diabetic control graded as good when the mean HbA_{1c} value was 10·5% or less, and poor when the mean HbA_{1c} was over 10·5%.

Statistical analysis comparing various indices of body fat with the quality of control (HbA_{1c}) was by the Mann-Whitney U test and probabilities of less than 0·05 were considered to be significant.

Results

The scatter of children's weights (figure), skinfold thickness, and relative standard weight percentiles were no different from those given in the Tanner charts. The mean annual HbA_{1c} concentration was 11·6% (range 7·2–17·2) (boys 11·4%, girls 11·9%). Thirty seven children (35%) had a mean annual

Table *Characteristics of good and poor diabetic control in 106 diabetic children*

	Good control (HbA_{1c} ≤10·5%)	*Poor control (HbA_{1c}>10·5%)*	*95% Confidence interval*
Mean age at diagnosis (years)	8·5	8·3	
Median absolute weight (kg)	53·1	50·0	−7·63 to 7·34
Mean duration (years)	6·1	6·6	
Median triceps skinfold (mm)	13·6	12·0	−3·0 to 1·6
Median subscapular skinfold (mm)	8·0	8·0	−1·0 to 2·0
Relative standard weight (%)	97·3	95·6	−7·30 to 5·20
Insulin dosage (U/kg/day)	0·9	0·9	

There were no significant differences between the groups.

HbA_{1c} concentration of 10·5% or less and 69 children (65%) had a mean annual HbA_{1c} concentration of more than 10·5%.

There were no significant differences in the median HbA_{1c} among those children whose absolute weight was more than 20% above the mean (median HbA_{1c} 11·9%), those whose relative weight was more than 120% (median HbA_{1c} 11·1%), or those whose skinfold thickness was more than 70% (HbA_{1c} 11·5%) when compared with their peers (median HbA_{1c} concentrations 11·6%, 11·6%, and 11·7%, respectively). The 95% confidence interval of the difference in medians was −1·20% to 1·15% for absolute weight, −1·7% to 1·2% for relative weight, and −1·2% to 1·0% for skinfold thickness. Conversely, no significant differences were found between those with good as opposed to poor control and the various indices of obesity (table).

Discussion

Any definition of obesity is arbitrary as the distribution of weight in the general population does not segregate into distinct populations of obese and nonobese. Furthermore, methods for evaluating fatness cannot be compared directly and thus it is not easy to derive acceptable criteria for the diagnosis.[3] Direct methods for the measurement of body fat are generally invasive, but it can be measured indirectly by estimating skinfold thickness, and it is this pain free and non-invasive method that is generally used in children.

We are unaware of any publications on the incidence of obesity in childhood diabetes, or on its effect on diabetic control. Many paediatricians believe, however, that children with diabetes are often overweight and that this may have a deleterious effect on their diabetic control. We have found the scatter of the children's weights to be no different from those of the standard national weight charts, and only 9% of children had weights in excess of 120% of relative weight compared with a mean relative weight of 117% in adults with insulin dependent diabetes.[4]

Obesity affecting mainly the upper half of the body correlates with increased atherogenic and diabetogenic mortality and should be considered more seriously than obesity that predominantly affects the hips and lower limbs.[5] In this study 20% of the children had excess fat affecting the upper half of the body. We found no evidence, however, of poorer diabetic control among them, and no correlation between skinfold thickness and HbA_{1c} concentration.

Obesity leads to insulin resistance, but we have no evidence to suggest that this is the case in the obese children as their mean insulin dosage—U/kg body weight—and their mean HbA_{1c}% were similar to those among non-obese diabetic children.

Our diabetic population is not obese and this may reflect the high fibre, low fat diet prescribed in our clinic. As work in adults has confirmed an association between obesity, poor diabetic control, and diabetic complications, it is important to emphasise the prevention of excessive weight gain.

We are grateful to Dr AO Hughes for statistical advice.

References

[1] Hundley JM. Diabetes—overweight: US problems. *J Am Diet Assoc* 1956;**32**:417–22.

[2] Tanner JW, Whitehouse RH. Revised standard for triceps and subscapular skinfolds in British children. *Arch Dis Child* 1975; **50**:142–50.

[3] Sims EAH. Definition, criteria and prevalence of obesity. In: Bray GA, ed. *Obesity in America.* NIH publication No 79–359. Washington: US Government Printing Office, 1979:20–36.

[4] Perkins MR, Plehwe WE, Hosking MN, Tartle JR. A high prevalence of obesity in diabetic population: results of survey of food pattern in 252 patients in a 2 year period. *Diabetes Res Clin Pract* 1985;**1**:9–20.

[5] Vague J, Combes R, Tramoni M, *et al.* Clinical features of diabetogenic obesity. In: Vague J, Vague P, eds. *Diabetes and obesity.* International Congress series No 454. Amsterdam: Excerpta Medica, 1979:127–47.

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Increased concentration of aluminium in the brain of a parenterally fed preterm infant

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SUMMARY Parenteral feeding solutions currently used for preterm infants are contaminated with aluminium. We report the case of an infant who was fed parenterally for 45 days, who died aged 3 months, and who had a considerably increased concentration of aluminium in his brain tissue at necropsy.

Aluminium toxicity occurs in patients with renal failure who require haemodialysis[1] or who receive aluminium hydroxide as a phosphate binding agent.[2] It presents as anaemia, poor bone mineralisation and encephalopathy ('dialysis dementia'). Preterm infants receiving parenteral nutrition are at risk of toxicity because of reduced renal function, and reported high levels of contamination of their parenteral feeding solutions.[3]

We describe the case of a preterm infant who received parenteral nutrition for 45 days, and who had repeated unexplained convulsions.

Case report

The baby boy was born at 24 weeks' gestation, weighing 630 g. Intermittent positive pressure ventilation was started at the age of 6 hours, initially for respiratory distress and subsequently for apnoea during episodes of sepsis. Bilateral intraventricular haemorrhages with right sided periventricular leucomalacia were diagnosed by ultrasound scan on day 7.

Parenteral nutrition was given from days 1 to 25 and days 47 to 68 because of respiratory distress, sepsis, and intolerance of enteral feeds. The solutions used were Vamin 9 glucose with mineral, trace element, and water soluble vitamin additives, and Intralipid 10% with fat soluble vitamins.

Convulsions first occurred on day 10. Full investigations to diagnose metabolic abnormalities and the presence of sepsis were carried out, including lumbar puncture, which showed an excess of leucocytes in the cerebrospinal fluid. Benzylpenicillin and chloramphenicol were given for 10 days, although no organism was cultured. Phenobarbitone was given until day 37 when because there had been no further convulsions it was reduced, and then discontinued.

Convulsions recurred on day 69. No evidence of sepsis or metabolic disturbance was found. Ultrasound scanning showed moderate bilateral ventricular dilation, more obvious on the right side, but no other structural abnormality. Phenobarbitone was recommenced, and a 24 hour electroencephalogram one week later showed no abnormal activity. The anticonvulsant treatment was reduced, and discontinued on day 86.

The absence of a convincing explanation for the convulsions (other than structural damage from intraventricular haemorrhages and periventricular leucomalacia) led us to consider the possibility of aluminium toxicity as a result of parenteral feeding. Before investigations could be instituted, however, the infant had further convulsions; again, no cause was found. The infant died two days later aged 93 days.

At necropsy samples of temporoparietal grey matter were taken for analysis for the presence of aluminium. The avoidance of contamination is of paramount importance in aluminium estimations, and attention was paid to avoiding potential hazards; the pathologist removed glove dust by careful washing before handling samples, specimens were taken by sectioning with an unused scalpel, and placed immediately in plastic containers. No processing of samples was done, other than freezing; they were thawed immediately before being digested by nitric acid. Analysis was by direct injection into a Perkin Elmer Zeeman 3030 atomic absorption spectrophotometer.

Samples of temporoparietal grey matter from 12 infants who had died suddenly and unexpectedly in the first year of life were analysed for comparison. The aluminium contents of parenteral nutrition solutions have been previously published.[3] Aluminium intake was calculated as the mean aluminium content of each component solution multiplied by the volume given for each day during periods of parenteral feeding.

RESULTS OF ANALYSIS

The average aluminium intake was 14 µg/day. Total intake of aluminium from intravenous feeding solutions was 645 µg. Additional aluminium may have been given with intravenous drugs and plasma, and with oral feeds.[3]

The aluminium content of the subject's grey matter was 40·1 µg/g wet weight of tissue; the mean (SD) value for 12 infants dying unexpectedly within the first year of life was 2·4 (1·6) µg/g wet weight of tissue. The fat content of the brain doubles during the first year of life; this would not however, account for the 20 fold difference in brain aluminium concentrations observed. In addition, aluminium accumulates specifically in cortical grey matter, the fat content of which is less likely to vary with age.

Discussion

The preterm infant studied here had a brain aluminium content of 40 µg/g wet weight of tissue. In 'dialysis dementia', corresponding cortical aluminium concentrations are reported to be 20–30 µg/g in adults,[1] and even lower in infants.[2 4]

Toxicity is not proved by the finding of a high brain aluminium content. Nevertheless, with a history of unexplained convulsions and prolonged intravenous feeding, there is a strong possibility that high aluminium intake was at least a large contributory factor.

Parenterally administered aluminium is poorly excreted by preterm infants, who retain up to 80% of an intravenous load.[5] Calcium gluconate, potassium acid phosphate, and the trace element solution (Ped-El) together accounted for 90% of the contamination. The substitution of calcium chloride for calcium gluconate reduces delivery of aluminium by 70% from an average intake of 30 µg/kg/day when on full intravenous feeding at 150 ml/kg/day to 8 µg/kg/day. The lower value of 14 µg/kg/day for the index case was due to partial enteral feeding.

The signs of aluminium toxicity, which include encephalopathy, anaemia, and poor bone mineralisation, are common complications of many diseases in sick premature babies. Nevertheless, we suggest that when conventional therapeutic manoeuvres fail, aluminium toxicity should be considered.

References

1. Van de Vyver FL, De Broe ME. Aluminium in tissues. *Clin Nephrol* 1985;**24**(suppl 1):S37–S57.
2. Randell ME. Aluminium toxicity in an infant not on dialysis. *Lancet* 1983;**i**:1328–9.
3. McGraw M, Bishop N, Jameson R, *et al.* Aluminium content of milk formulae and intravenous fluids used in infants. *Lancet* 1986;**i**:157.
4. Freundlich M, Zillervelo G, Faugere MC, Abitbol C, Strauss J, Malluche HH. Infant formulae as a cause of aluminium toxicity in neonatal uraemia. *Lancet* 1985;**ii**:527–9.
5. Sedman AB, Klein GL, Merritt RJ, *et al.* Evidence of aluminium loading in infants receiving intravenous therapy. *N Engl J Med* 1985;**312**:1337–43.

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Gowers' sign revisited

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SUMMARY We studied the patterns of standing in children with neuromuscular disorders and central hypotonia for Gowers' sign, and compared these two groups with healthy controls. More children with central hypotonia than controls rolled prone before standing at 36 months; at this age all children with neuromuscular disorders rolled prone. Neurological assessment is indicated in children continuing to roll prone before standing at 3 years.

In 1879 Gowers first described the pattern of standing in 21 boys with pseudohypertrophic muscular paralysis in a clinical lecture to the students of University College.[1] He initially thought this pattern of standing was pathognomonic for children with this condition as it was present in all his ambulatory cases. It has subsequently been shown to be present in other children with proximal muscle weakness.

Dr Gowers' eloquent description of the pattern of standing, which now bears his name, emphasised two important features (figure): (i) the children adopting a prone position on all fours before attempting to stand and (ii) the children 'walking up their legs'. It is the second feature that is often quoted in textbooks and remembered by physicians as Gowers' sign.

The Muscular Dystrophy Group report that the

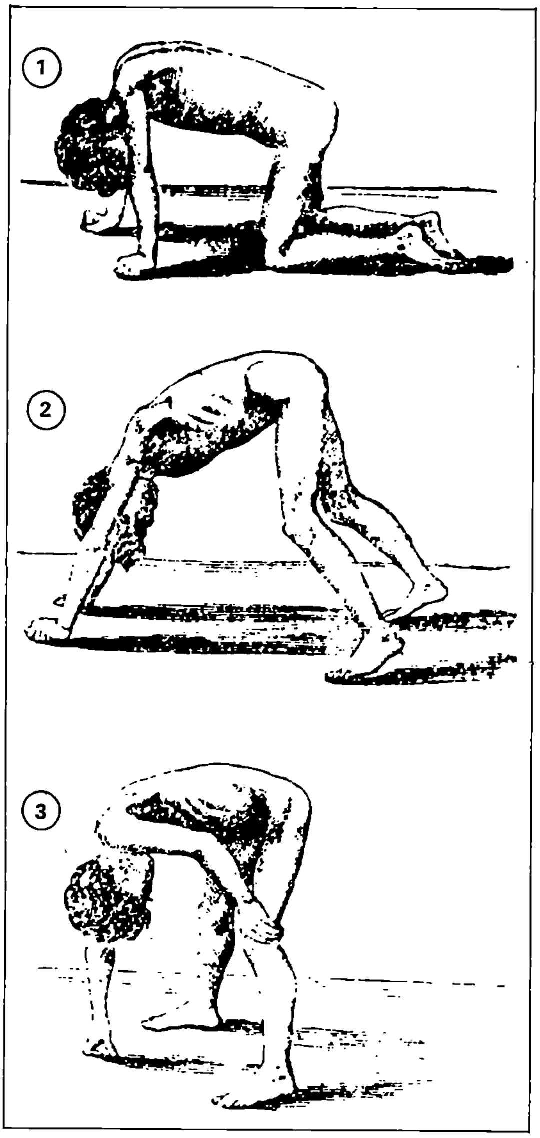

Figure *Gowers' sign. Reproduced with kind permission of the publishers from WR Gowers. Clinical lecture on psuedohypertrophic muscular paralysis. Lancet, 1879.*[1]

mean age for diagnosis of boys with Duchenne muscular dystrophy is 5·2 years whereas parents first present their children to doctors at a mean age 2·7 years.

We believe the mean delay in diagnosis of 2·5 years is largely due to doctors failing to recognise the salient feature of Gowers' sign—that is, the child adopting a prone position before standing. It is only when proximal leg weakness becomes most pronounced that children 'walk up their legs'.

The adoption of a prone position before standing can also be seen as a normal developmental phase in toddlers. This study defines the age at which children cease to turn prone while rising to a standing position and then examines the pattern of standing in children known to have neuromuscular disorders or central hypotonia.

Patients and methods

The study group consisted of 23 children aged 27–90 months (mean 58 months) with neuromuscular disorders and 26 children aged 16–69 months (mean 37 months) with central hypotonia. These children were consecutive new referrals seen by GBW at paediatric neurology and neuromuscular clinics at the Royal Manchester and Booth Hall Children's Hospitals.

The children with central hypotonia had no evidence of a neuromuscular disorder on clinical, neurophysiological, and in some cases, histopathological grounds. Controls consisted of 175 healthy children aged 13–60 months (mean 31·5 months) examined at district community child health centres.

The pattern of standing was defined by asking each child to lie supine and then to stand as quickly as they could on three seperate occasions. Results were analysed according to whether the child adopted a prone position on two of those occasions at any time during standing. Frequencies between groups were compared using χ^2 analysis or Fisher's exact test where appropriate.

Results

Eighteen of 95 controls (19%) adopted a prone position as they stood at age 30 months or more; by 36 months only four of 63 (6·5%) rolled prone. Significantly more children with central hypotonia rolled prone, 15 of 20 (75%) at 30 months ($p<0\cdot001$) and eight of 13 (61%) at 36 months ($p<0\cdot001$). At

Table *Pattern of standing in children* ≥ 36 *months. Results are No (%)*

	Controls (n=59)	*Neuromuscular disorder or central hypotonia (n=34)*
Rolls prone:		
Yes	4 (7)	29 (85)
No	55 (93)	5 (15)

$\chi^2=66$, $p=<0\cdot001$.

no age did the group with neuromuscular disorders stop rolling prone when attempting to stand.

When the combined groups with neuromuscular disorders and central hypotonia were compared with controls the age of 36 months was significantly discriminating in distinguishing normal children from those with underlying neurological abnormality (table).

Discussion

Our study emphasises the salient features of Gowers' sign and its importance in identifying children with neuromuscular disorders and central hypotonia. It is easily performed and can readily be incorporated into screening examinations of children.

We suggest that if children continue to roll prone when attempting to stand at 30 months special attention should be paid to them. If they continue to roll prone at 3 years of age a full neurological assessment is warranted.

Reference

[1] Gowers WR. Clinical lecture on pseudohypertrophic muscular paralysis. *Lancet* 1879;ii:73–5.

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Controversy

Diagnosis of coeliac disease: time for a change?

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Diagnosing coeliac disease is not easy. Current recommendations stem from a 1970 statement of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)[1] and call for: histological evidence of the lesion; evidence of its disappearance after an adequate period on a gluten free diet; and evidence of its recurrence after the reintroduction of gluten into the diet. Such a procedure, which seems to be widely accepted in Europe,[2] is probably optimal for a firm diagnosis, but has several drawbacks, particularly in the light of new developments that have since taken place. Firstly, the time required for the final diagnosis is unduly long (three years on average); secondly, it does not take into account the variability in clinical expression of the disease; thirdly, it does not take into account the fact that after the age of 2 years it is highly unusual for subtotal villous atrophy to be caused by diseases other than coeliac disease[2]; and, fourthly, it means re-exposing a child to the offending agent in order to reproduce the mucosal damage. Furthermore, even this challenge (which is now known to be potentially harmful to the child's growing potential[3 4]) might be inconclusive, as evidence is now mounting that relapse may take longer than two years.[2 5 6]

It is therefore not surprising that several workers have started to adopt a somewhat more flexible attitude to the diagnosis that takes into account some new laboratory investigations (particularly the presence of antigliadin antibodies) and improved knowledge of the clinical range of the disease that has been acquired since the diagnostic protocol was introduced almost 20 years ago.

For these reasons, the Italian Working Group for Paediatric Gastroenterology (which was formed in 1976 and has 250 members) undertook an evaluation of the current approach to the diagnosis of coeliac disease in Italy to verify whether a simplified, more flexible approach was possible. The following points were retrospectively assessed, in a total of 3138 patients with coeliac disease from 33 different centres: (i) the importance of human leucocyte antigen (HLA) typing and the presence of antigliadin antibodies; (ii) the need for repeated intestinal biopsy in so called 'atypical' cases or in cases presenting in older children; (iii) the predictive value of the presence of 'flat mucosa' in a child with clinical or laboratory evidence, or both, suggesting coeliac disease; and (iv) the feasibility and evaluation of gluten challenge.

The collected data were analysed and presented by invited experts in a two day meeting in Trieste in May 1987. During the meeting each point was discussed and a final consensus was reached, in a session chaired by A Rubino. The most important points are summarised below.

Importance of HLA typing

A total of 324 patients, all of whom were diagnosed according to the strict criteria of the ESPGAN protocol, have had HLA typing carried out (table 1). HLA class II types are found more often in patients with coeliac disease which confirms work from the rest of Europe.[7–10] The predictive value of these is limited, however, as such antigens may also be found in healthy controls, and they are not always present in patients. In our series, 7·7% of patients with coeliac disease did not have either HLA-DR3 or HLA-DR7. If HLA-DQ2 is also considered, this figure decreases to 5%. It should be noted, however, that even the patients with coeliac disease who did not have HLA-DQ2 or HLA-DR3 and HLA-DR7, or both, have so far all had HLA-DR4 isolated from their plasma.

From the point of view of the diagnosis, therefore we can conclude that the finding of one of these

Table 1 *Association between HLA type and coeliac disease*

Country (No of cases)	*HLA-DR3 (%)*	*Relative risk*	*HLA-DR7 (%)*	*Relative risk*	*HLA-DR3 and DR3-DR7 (%)*	*Relative risk*
Ireland[7] (92)	86	9·2	25	0·7	21	4·3
Germany[8] (42)	64	7	48	2·7	26	7·5
France[9] (22)	63·7	6·6	54·5	4·5	—	—
Spain[10] (163)	71·2	11·5	61·4	2·6	38	11·5
Italy (324)	61	6·3	53·7	3·4	22·5	10·5

antigens, although consistent with the diagnosis of coeliac disease, can not be assumed to prove it. On the contrary if no such antigens are found, this is of great diagnostic importance, because it implies that coeliac disease can confidently be ruled out.

Importance of antigliadin antibodies

One of the most important discoveries in the last few years has been the method for detection of serum antigliadin antibodies in patients with coeliac disease. Although the method is not yet standardised, and its discriminating capabilities are not yet confirmed, it looks as if it will be a useful diagnostic tool. To calculate their importance and define their diagnostic role, data on serum antigliadin antibodies detected in the various phases of the diagnostic procedure laid down in the ESPGAN protocol were analysed. The collected data (table 2) refer to children who were in phase I (359 cases of florid disease, while on a gluten-containing diet), in phase II (452 cases in clinical remission while on a gluten free diet), in phase III (286 patients being challenged with a diet containing gluten), 880 controls who were age matched patients with various gastrointestinal disorders not accompanied by flat mucosa, and 496 healthy children.

The sensitivity of IgG antigliadin antibodies comes close to 100% in patients in phase I; on the other hand, IgG antigliadin antibodies are detected in a comparatively high percentage (21·7%) of patients with other gastrointestinal disorders. For IgA antigliadin antibodies they show a somewhat lower sensitivity (90·5%), but a better specificity, being present in only 3% of patients who do not have coeliac disease. It should not be forgotten that the incidence of IgA deficient subjects (which obviously reduce the number of subjects with IgA antigliadin antibodies) is about 2–3% in patients with coeliac disease—that is, much higher than in the general population.

Finally, the specificity of antigliadin antibodies when tested against healthy controls is high. We believe that these conclusions are true, despite the fact that the methods used differed among the centres (enzyme linked immunosorbent assay (ELISA) in most, immunofluorescence in a few). Our conclusion is based on the large sample size, and the consistency of the results compared with most other reported series.[11–13]

Another test widely used for the diagnosis of coeliac disease is the one hour blood D-xylose absorption test. When considered alone in our patients, this test agreed with the jejunal histology in 70%. When the xylose test was used in combination with estimation of antigliadin antibodies, however,

Table 2 *Antigliadin antibodies in patients with coeliac disease and in controls*

	Diagnostic phase No of patients	*Total No (%) with antigliadin antibodies*	*No (%) with IgA antigliadin antibodies*	*No (%) with IgG antigliadin antibodies*
Patients with coeliac disease:				
I	359	353 (98·3)	325 (90·5)	351 (98·0)
II	452	185 (40·9)	53 (11·7)	181 (40·0)
III	286	269 (94·0)	236 (82·5)	262 (91·6)
Patients with other gastrointestinal disease	880	197 (22·3)	27 (3·0)	191 (21·7)
Healthy controls	496	17 (3·4)	3 (0·6)	14 (2·8)

the agreement of both tests with the histological picture was 98% in a series of 48 recently diagnosed patients.

In summary, the diagnostic accuracy of estimating antigliadin antibodies is quite high: almost no patients with florid coeliac disease lack IgG antigliadin antibodies, and few patients who have IgA antigliadin antibodies do not have coeliac disease. Furthermore, when they are used together and are both positive, serum antigliadin antibodies and blood xylose testing seem to be consistent with the jejunal morphology of the patient with coeliac disease.

Cases that are 'atypical' or present in older children, or both

Data regarding age and mode of onset were obtained from 1126 patients with coeliac disease. Ninety four (8·4%) were labelled 'atypical', as they did not present with diarrhoea. Their mean age at onset of symptoms was 2·9 years (significantly higher than in typical cases). Characteristically they commonly presented with iron deficiency anaemia, failure to grow and put on weight, anorexia, vomiting (often specifically related to gluten-containing meals), and constipation. In a further group of 44 patients (3·9%), the symptoms began after the age of 2 years (late onset coeliac disease), at a mean age of 6·2 years. Again, among other symptoms, half these older children presented with short stature.

Considering the time elapsing between onset of symptoms and first biopsy (on average 3·8 years in the series of 94 'atypical' patients, 3·6 in the 44 late onset patients), it is evident that the mean age is much higher—6·7 years for the former group of patients with coeliac disease, 9·8 for the latter. At these ages, and in our geographical area, there is practically no differential diagnosis for subtotal villous atrophy responding to gluten withdrawal. A particular subgroup of 'atypical' patients with coeliac disease comprises those affected by dermatitis herpetiformis (Duhring's disease). They can be diagnosed with full confidence from a skin biopsy specimen by an experienced dermatologist,[14] thus obviating the need for intestinal biopsy.

Diagnostic importance of the initial finding of subtotal villous atrophy in a child suspected of having coeliac disease

From the clinical records from 30 centres, we found that 3293 children underwent intestinal biopsy for suspected coeliac disease, and were found to have crypt hyperplastic subtotal villous atrophy. Among them, 3138 (95%) were eventually diagnosed as having coeliac disease after completing the full diagnostic procedure. It should be emphasised that 2400 of them strictly followed the diagnostic phases of the ESPGAN protocol; the remaining 738 patients were diagnosed as having coeliac disease by 'simplified' diagnostic schemes, most of them omitting the second biopsy (table 3). Interestingly, the percentage of patients eventually diagnosed as having coeliac disease was no different among those who followed the ESPGAN protocol (95%) and those who did not (95·8%), suggesting an overlapping diagnostic accuracy between the rigid protocol and the more flexible attitude.

Focusing on the 155 patients (4·7%) in whom the diagnosis of coeliac disease was unconfirmed at the end of the diagnostic procedure, the following observations can be made: (i) the most common single diagnosis was cows' milk sensitive enteropathy (n=32, 20·6%), followed by transient gluten intolerance (n=24, 15·5%); (ii) the mean age of the patients at the time of first biopsy was 8 months, further highlighting the fact that the differential diagnosis of coeliac disease is essentially a problem of infancy; (iii) the data refer to patients that were, in most cases, seen at a time when estimation of antigliadin antibodies was not possible. It is therefore likely that that estimation could have improved the diagnostic value of the first biopsy.

These observations indicate that when facing a child whose history is consistent with coeliac disease and whose first biopsy specimen shows an unequivocal crypt hyperplastic subtotal villous atrophy, in our geographical area one has at least a 95% chance that one is dealing with coeliac disease: a diagnostic accuracy not too frequently found in paediatric practice. Furthermore, it is clear that adding the diagnostic weight of estimation of HLA and anti-

Table 3 *Association between 'flat mucosa' at first biopsy and eventual diagnosis of coeliac disease*

	No	%
All patients:		
Patients suspected of having coeliac disease with a 'flat mucosa'	3293	100
Eventual diagnosis of coeliac disease	3138	95·3
Other diagnoses	155	4·7
Diagnosis by strict adherence to ESPGAN protocol:		
Patients suspected of having coeliac disease with a 'flat mucosa'	2523	100
Eventual diagnosis of coeliac disease	2400	95·1
Other diagnoses	123	4·9
Diagnosis by other 'simplified' procedures:		
Patients suspected of having coeliac disease with a 'flat mucosa'	770	100
Eventual diagnosis of coeliac disease	738	95·8
Other diagnoses	32	4·2

gliadin antibodies will further increase that percentage, particularly by omitting false positive diagnoses.

Methods of gluten withdrawal and reintroduction: clinical and diagnostic implications

Table 4 shows the data concerning age at diagnosis and duration of the diagnostic phases in 361 patients with coeliac disease; these are the 15 most recently diagnosed patients from each centre. The mean age of diagnosis (3·2 years) seems somewhat higher than in the past, in accordance with the present trend of the disease as reported by others.[15] Mean duration of the gluten free diet seems quite long, even longer than that recommended by the ESPGAN protocol, thus increasing the likelihood of poor compliance to the diet and delaying the time to conclusive diagnosis. Most important, however, is the duration of challenge (seven months), which seems too long. In most patients the mucosal relapse occurs within three months,[16 17] although individual variations in the speed of mucosal relapses are well recognised, and in the occasional patient a particularly long time may elapse.[5]

In any case, prolonging the duration of the challenge in the patients with coeliac disease does not seem to be of any benefit: the histological, clinical, and biochemical data from 195 patients with coeliac disease show that the bulk of laboratory results (excluding estimation of antigliadin antibodies) and the clinical response do not correlate with histological signs of relapse. Only in 48·8% of our cases did such a correlation exist, similar to what has previously been reported by others.[6 16 17] Thus prolonging gluten challenge does not help in providing clear cut evidence on which to decide the time for biopsy and in addition has harmful effects on the child's weight and growth. Recent evidence, on the other hand, indicates that antigliadin antibodies rise within a few weeks of the reintroduction of gluten.[18] Thus by monitoring the rise in antigliadin antibodies, most challenges may be stopped after 60 days.[18]

If we consider that 95% of the patients are already correctly diagnosed after the first biopsy, and that this figure may only increase by the use of estimations of antigliadin antibodies, to link the final diagnosis to the outcome of the challenge might actually result in underdiagnosis of the disease. On one hand, the support offered by clinical and laboratory data is poor, and on the other hand, it is well known that a number of patients do develop the mucosal lesion late.[5 6] Finally, it must not be forgotten that a prolonged challenge, particularly during periods of increased growth (infancy and adolescence), may interfere with linear growth.[3 4] The bulk of this evidence would then suggest that a gluten challenge is not necessary for diagnosis and may actually prove to be harmful.

Table 4 *Age and diagnostic phases of coeliac disease in 361 selected patients*

	No of patients	*Mean (range)*
Age at diagnosis (years)	361	3·2 (0·4–26)
Duration of gluten free diet (months)	322	17·7 (3–78)
Age at challenge (years)	320	5·1 (1·5–25·2)
Duration of challenge (months)	319	7·0 (0·2–71)

Conclusions

After having carefully evaluated and thoroughly discussed all the evidence that has been outlined briefly above, the Working Group for Gastroenterology came to the following conclusions: (1) in many instances of suspected coeliac disease (and in our geographical area) the diagnostic approach may differ from that recommended in the ESPGAN protocol. It must be firmly stated, however, that at present no diagnosis of coeliac disease can be made without the characteristic histological picture of the duodenal-jejunal mucosa. (2) In cases presenting with a history and clinical picture suggestive of coeliac disease, laboratory data (including antigliadin antibodies) consistent with coeliac disease, a clear histological picture of a crypt hyperplastic subtotal villous atrophy, an obvious clinical and laboratory response to the gluten free diet, and as long as the diagnosis of cows' milk sensitive enteropathy can be ruled out, the definitive diagnosis of coeliac disease can be made. On this basis, gluten must be permanently excluded from the diet, and regular follow up should be instituted.

Whenever the diagnosis is uncertain on the basis of history or clinical or laboratory evidence, or both, or the appearance of the mucosa at initial biopsy is considered doubtful, strict adherence to the ESPGAN protocol is recommended (including gluten challenge to be carried out at an early age), with the possible exception that the second biopsy may be omitted, provided that all pertinent data (including estimation of antigliadin antibodies) are in agreement.

Spontaneous gluten reintroduction is to be avoided by all costs. Whenever, in order to prevent it, or in accordance with family pressure, it is decided to perform a medically supervised gluten challenge, it is recommended that such a challenge should not be done during the pubertal spurt of infantile growth and that the diet containing gluten is maintained for no longer than three months in the first instance. Evaluation of relapse may, but does not necessarily have to, be confirmed histologically; such confirmation may not be needed when clinical and laboratory evidence (including a rise in antigliadin antibodies titre) is clear.

These considerations and recommendations are reported as a matter for further discussion and in the hope that they will stimulate comments and criticism from all paediatricians who take part in investigation or clinical management, or both, of young patients with coeliac disease.

The data summarised here were collected at the following centres: Clinica Pediatrica dell'Universita', Ancona; Istituto di Pediatria Clinica e Sociale, Universita' di Bari; Divisione di Pediatria, Ospedale Maggiore 'GA Pizzardi' Bologna; Istituto Clinica e Biologia Eta' Evolutiva dell'Universita' Cagliari; Clinica Pediatrica dell'Universita' di Catania; Clinica Pediatrica Ia dell'Universita'; Istituto G. Gaslini, Genova; Divisione Pediatrica, Ospedale Generale, Mantova; Clinica Pediatrica IIa dell'Universita' di Messina; Clinica Pediatrica Ia, Universita' di Milano; Clinica Pediatrica IIa, Universita' di Milano; Clinica Pediatrica IIIa, Universita' di Milano; Clinica Pediatrica IVa—Ospedale 'L Sacco', Milano; Clinica Pediatrica Ia dell'Universita' di Modena; Divisione Pediatrica, Ospedale G Salesi, Ancona; Divisione Pediatrica, Ospedale degl Esposti, Bologna; Divisione Pediatrica, Ospedale Bufalini, Cesena; Divisione Pediatrica, Ospedale S Michele, Cagliari; Divisione Pediatrica, Ospedale S Carlo, Milano; Dipartimento di Pediatria dell'Universita' di Napoli; Divisione Pediatrica, Ospedale SS Annunziata, Napoli; Clinica Pediatrica, Universita' di Padova; Divisione Pediatrica, Ospedale dei Bambini, 'G Di Cristina', Palermo; Clinica Pediatrica dell'Universita' di Parma; Clinica Pediatrica dell'Universita' di Pavia; Clinica Pediatrica I, Universita' La Sapienza, Roma; Clinica Pediatria III, Universita' la Sapienza, Roma; Clinica Pediatrica dell'Universita', Torino; Clinica Pediatrica dell'Universita', Trieste; Servizio Pediatrico Speciale, Ospedale Borgo Trento, Verona; Divisione Pediatrica, Ospedale infantile Alessandri, Verona; Clinica Pediatrica dell'Universita', Palermo; Clinica Pediatrica IIIa Universita' di Bologna; Ospedale Bambino Gesu', Roma; and Clinica Pediatrica dell'Universita', Verona.

References

[1] Meeuwisse GW. Round table discussion. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59**:461–3.

[2] McNeish AS, Harms HK, Rey J, Shmerling DH, Visakorpi JK, Walker-Smith JA. The diagnosis of coeliac disease. *Arch Dis Child* 1979;**54**:783–6.

[3] McNeish AS. Coeliac disease duration of gluten free diet. *Arch Dis Child* 1980;**55**:110–1.

[4] Bresson JL, Schmitz KW, Rey J. Characteristics of relapse in coeliac disease. *Acta Paediatrica Belgica* 1980;**33**:270.

[5] Shmerling DH, Franckx J. Childhood coeliac disease. A long term analysis 106 of relapse in 91 patients. *J Pediatr Gasroenterol Nutr* 1986;**5**:565–9.

[6] Kuitunen P, Savilahati E, Verkasalo M. Late mucosal relapse in a boy with coeliac disease and cows' milk allergy. *Acta Paediatr Scand* 1986;**75**:340–2.

[7] McKenna R, Stevens FM, McNicholl B, Scholz S, Albert E, McCarthy CF. Family and population studies of HLA and coeliac disease in the West of Ireland. *Tissue Antigens* 1983;**22**: 175–81.

[8] Albert E, Harms K, Bertele R, *et al.* B-cell alloantigens in coeliac disease. In: McNicholl B, McCarthy CF, Fottrell PF, eds. *Perspectives in coeliac disease.* Lancaster: MTP Press, 1978:123–9.

[9] Betuel H, Gebuhrer L, Descos L, Percebois H, Minaire Y, Bertrand J. Adult coeliac disease with HLA-DRw3 and -DRw7. *Tissue Antigens* 1980;**15**:231–8.

[10] Mearin ML, Biemond I, Pena AS, *et al.* HLA-DR phenotypes in Spanish coeliac children: their contribution to the understanding of the genetics of the disease. *Gut* 1983;**24**:532–7.

[11] Savilahti E, Viander M, Perkkio M, *et al.* IgA antigliadin antibodies: a marker of mucosal damage in childhood coeliac disease. *Lancet* 1983;**i**:320–2.

[12] Unsworth DJ, Walker-Smith JA, Holborow EJ. Gliadin and reticulin antibodies in childhood coeliac disease. *Lancet* 1983;**i**: 874–5.

[13] Volta U, Lenzi M, Cassani F, *et al.* Gliadin antibodies in coeliac disease. *Lancet* 1983;**i**:1285.

[14] Ermacora E, Prampolini L, Gelmetti C, *et al.* Long term follow-up of dermatitis herpetiformis in children. *J Am Acad Dermatol* 1986;**15**:24–30.

[15] Maki M, Kallonen K, Lahdeaho ML, *et al.* Changing pattern of childhood coeliac disease in Finland. *Acta Paediatr Scand* 1989 (in press).

[16] Hamilton JR, McNeill LK. Childhood coeliac disease: response of treated patients to a small uniform daily dose of wheat gluten. *J Pediatr* 1972;**81**:885–93.

[17] Kumar P, O'Donoghue DP, Lancaster-Smith M. Cellular changes in the jejunal mucosa following the re-introduction of gluten in treated coeliac disease. In: Pepys J, Edwards AM, eds. *The mast cell—its role in health and disease.* Tunbridge Wells: Pitman Medical, 1979:647–62.

[18] Auricchio S, Greco L, Troncone R. Gluten-sensitive enteropathy in childhood. *Pediatr Clin North Am* 1988;**35**:157–87.

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Commentary

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The 'cause' of coeliac disease is not yet known in molecular terms. The diagnosis of coeliac disease remains empirical and is currently based on two well established facts. The first is that gluten causes a malabsorption syndrome with small bowel enteropathy in susceptible subjects.[1] Secondly, withdrawal of gluten from the diet leads to complete restoration to normal of the patient and his intestinal mucosa.[2]

A third important contribution to our thinking about coeliac disease was provided by the (then) European Society for Paediatric Gastroenterology (ESPGA) in its publication of the 'Interlaken criteria'.[3] In these criteria, coeliac disease was affirmed to be a permanent condition of gluten intolerance, and it was implied that, in order to substantiate an initial diagnosis of coeliac disease, the permanence (or at least persistence) of gluten intolerance should be confirmed in each individual patient by carrying out one or more gluten 'challenges'. Such challenges, stated ESPGA, should lead to a recurrence of the mucosal lesion within two years.

This expanded definition of coeliac disease has been influential and many European centres have used it to the letter.[4] There have been problems, however, both theoretical and practical. Firstly, colleagues in France showed that sensitivity of the mucosa to gluten can vary with age,[5] and Egan-Mitchell *et al* in Ireland described coeliac children in whom the mucosal lesion of coeliac disease did not recur until five or more years after gluten reintroduction.[6] Secondly, and at a practical day to day level, there has been an understandable reluctance by both parents and paediatricians to reintroduce 'forbidden fruit' into the diet, both because of the harm it might cause and the habits it might engender. Surreptitiously, corners have been cut.

The Italian Working Group for Paediatric Gastroenterology has rendered a valuable service in the present paper by analysing what has actually been happening in 33 paediatric centres and what the outcomes have been. The authors are able to compare an unprecedentedly large series of 2400 patients diagnosed as coeliac by the full ESPGA(N) criteria, with 738 whose diagnosis was made by a simplified route. Even though allowance must be made for the fact that no attempt was made to standardise observations among centres (for example, the histological reports were accepted at face value by the Group, and different assay systems for antigliadin antibodies were used), the sheer volume of data commands serious attention.

The conclusions and recommendations are eminently sensible. Firstly, if the clinical picture suggests coeliac disease (and cows' milk intolerance can be excluded) and the jejunal mucosa shows crypt hyperplastic subtotal villous atrophy, and secondly, if there is an obvious clinical response to a gluten free diet, the diagnosis can confidently be assumed to be coeliac disease and a lifelong gluten free diet should be instituted. My only warning to those who wish to adopt this practice is to make sure that the histological lesion is confirmed by a histopathologist who is accustomed to interpreting paediatric intestinal biopsy specimens. The commonest reason seen in our clinic in Birmingham for the erroneous diagnosis of coeliac disease made elsewhere has been overinterpretation of minor histological changes in the mucosa by a histopathologist more accustomed to viewing tissue from adults.

In theory this 'no gluten challenge, no further biopsies' approach could mistakenly diagnose as coeliac disease a case of temporary gluten intolerance.[7] Such cases are, however, rare, and becoming rarer, and usually arise in young infants with a short history, and sometimes with evidence of other food sensitivities as well.

Lastly, the authors confirm the observation of others that the rise and fall of antigliadin antibodies in the blood can be useful in the initial diagnosis, in monitoring the response to gluten withdrawal, and in measuring the response to a gluten challenge. There is no evidence in the literature to suggest how, or if, antigliadin antibodies are causally related to the signs and symptoms of coeliac disease, but even if these antibodies prove to be epiphenomena, their serial measurement can give useful diagnostic help in difficult cases.

However the diagnosis of coeliac disease is reached, it is essential to undertake long term follow up by handing on one's patients with coeliac disease to an adult gastroenterologist at an appropriate age. Dietary compliance over a lifetime is probably not achieved in many cases[8] and the longterm morbidity in those who break their diet is still uncertain.

References

1 Sakula J, Shiner M. Coeliac disease with atrophy of the intestinal mucosa. *Lancet* 1957;**ii**:876–7.

2 Anderson CM. Histological changes in the duodenal mucosa in coeliac disease. Reversibility during treatment with a wheat gluten free diet. *Arch Dis Child* 1960;**35**:419–27.

3 Meeuwisse GW. Round table discussion. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59**:461–3.

4 McNeish AS, Harms HK, Rey J, Shmerling DH, Visakorpi JK, Walker-Smith JA. The diagnosis of coeliac disease. *Arch Dis Child* 1979;**54**:783–6.

5 Schmitz J, Jos J, Rey J. Transient mucosal atrophy in confirmed coeliac disease. In: McNicholl B, McCarthy CF, Fottrell PF, eds. *Perspectives in coeliac disease.* Lancaster: MTP Press, 1978:259–66.

6 Egan-Mitchell B, Fottrell PF, McNicholl B. Prolonged gluten tolerance in treated coeliac disease. In: McNicholl B, McCarthy CF, Fottrell PF, eds. *Perspectives in coeliac disease.* Lancaster: MTP Press, 1978:251–7.

7 McNeish AS, Rolles CJ, Arthur LJH. Criteria for diagnosis of temporary gluten intolerance. *Arch Dis Child* 1976;**51**:275–8.

8 McCrae WM, Eastwood MA, Martin MR, Sircus W. Neglected coeliac disease. *Lancet* 1975;**i**:187–90.

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Personal practice

Chronic idiopathic thrombocytopenic purpura: primum non nocere

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The vast majority of children with idiopathic thrombocytopenic purpura, dramatic though their signs may be at presentation, remit within weeks, with or perhaps despite medical attention. Such children, when referred to the Queen Elizabeth Hospital, Hackney Road by their family doctor, or appearing in the busy casualty department, have a careful history taken with particular emphasis given to the length of history, antecedent infections, and drugs. They are examined for evidence of bleeding, injury, enlargement of lymph nodes, liver, and spleen. A full blood count and coagulation screen are performed and the film is carefully examined. If there is the slightest doubt about the diagnosis or if specific treatment is contemplated a bone marrow aspiration is performed. Treatment involves a period of relative rest and the avoidance of aspirin. The parents are told that this is not leukaemia, that the risk of serious bleeding is very low, and that most children improve spontaneously within weeks to months. A follow up appointment is given to facilitate further discussion. Further active treatment is rarely indicated.

The debate about steroid treatment in acute idiopathic thrombocytopenic purpura)[1 2] has to a large extent been supplanted by that about the benefits of intravenous immunoglobulin,[3 4] now alas widely advertised as desirable treatment for acute idiopathic thrombocytopenic purpura. As the mortality of acute idiopathic thrombocytopenic purpura is less than 1% it would take a controlled trial of at least 14 000 patients to show a significant reduction in mortality,[5] and estimation of morbidity is difficult when symptoms usually remit before any alteration in platelet count. It is thus regrettable that a recent clinical trial comparing intravenous immunoglobulin and steroids did not include a control arm.[4 6] While it may be justifiable to give steroids or immunoglobulin (or both) as *a short term measure* to a child with serious bleeding or extensive mucous membrane haemorrhage at presentation, there is no firm evidence that either is beneficial or, as has been claimed, decreases the risk of chronic thrombocytopenia. Intravenous immunoglobulin is extremely expensive (approximately £30 per gram or £720 per course for a 15 kg child) and although heat treated, carries the theoretical risk of transmission of viral infections, particularly non-A non-B hepatitis.[7]

Chronic thrombocytopenia

Most children seen in a district hospital have acute thrombocytopenia. In the more rarefied atmosphere of the referral centre there appears a steady trickle of children with chronic thrombocytopenia. This somewhat arbitrary definition is traditionally applied to children with symptoms of longer than six months. The story of such patients is usually a variation on one of two themes. Either the child has a long history of easy bruising and eventually a blood count is performed and shows thrombocytopenia or there has been an acute onset, treatment with steroids, and apparent clinical improvements. After three or four weeks an attempt to reduce the steroids is followed by recurrence of bruising or perhaps just a fall in platelet count. Thus develops a repetitive cycle in which steroids are decreased and increased according to the platelet count, the parents become more anxious and the child more moody and cushingoid. A variation on the second theme is that steroids have been replaced by periodic intravenous immunoglobulin that may produce a temporary rise in platelet count. The management of these patients and their parents is a delicate task, requiring ample time for discussion and reassurance about anxieties which are, I am afraid, frequently iatrogenic.

It is obviously essential to be confident of the diagnosis. A story of bruising since infancy should prompt suspicion of one of the rare congenital thrombocytopenias, many of which present with low platelets and a cellular marrow with abundant megakaryotypes.[8] A careful inspection of the blood film, and when appropriate, tests of platelet function should exclude such a diagnosis. The finding of Döhle bodies in the neutrophils is a feature of the May-Hegglin anomaly, a rare autosomal dominant disorder associated with mild thrombocytopenia while small platelets with a history of affected males may suggest a forme fruste of Wiskott-Aldrich syndrome. The blood film in idiopathic thrombocytopenic purpura shows large platelets but the presence of numerous giant forms should arouse suspicion of the Bernard-Soulier syndrome, an autosomal recessive disorder of platelet function characterised by variable thrombocytopenia and by defective platelet aggregation with the antibiotic ristocetin.

Bone marrow examination is essential in the assessment of the child with chronic thrombocytopenia. If adequate slides are not available for review then an aspirate must be performed; if the slide does not show adequate megakaryocytes a trephine should be performed to assess marrow cellularity. Aplastic anaemia is rare in childhood but, particularly in the congenital marrow failures such as Fanconi's anaemia and dyskeratosis congenita thrombocytopenia may be the only abnormality in the blood count for many years.[9] The congenital abnormalities may be subtle or even absent in Fanconi's anaemia and mucosal atrophy and dystrophic nails often defy diagnosis in early dyskeratosis congenita. Once these conditions have been excluded how useful are other investigations in chronic thrombocytopenic purpura? Platelet associated immunoglobulin is raised in the vast majority of children with chronic idiopathic thrombocytopenic purpura but the availability of platelet serology has had little impact on the selection of treatment.[10] It is important, particularly in the older child, to investigate for the presence of other autoimmune disorders. While some children with chronic idiopathic thrombocytopenic purpura have subtle laboratory evidence of an immunoregulatory disorder few develop systemic lupus erythematosus or autoimmune haemolytic anaemia.[11]

Management of chronic idiopathic thrombocytopenic purpura

Chronic idiopathic thrombocytopenic purpura is usually a benign condition which does not require specific treatment and may remit at any time. Fifteen of a group of 150 children in Cleveland were still thrombocytopenic after one year but 11 of the 15 were asymptomatic and nine underwent spontaneous remission after two to 20 years.[12] There were no episodes of intracranial haemorrhage. In a long term study from Newcastle, 22 of 123 children remitted after one year, and three after five years.[13] There were two episodes of intracranial haemorrhage: one in retrospect due to probable consumptive coagulopathy and the other in a child with acute idiopathic thrombocytopenic purpura who was receiving steroids.[13] These reports reinforce clinical impressions of the natural history of chronic idiopathic thrombocytopenic purpura, but because they emanate from referral centres, probably underestimate the proportion of cases undergoing early remission.

Once the diagnosis is confirmed my main preoccupation is to thus ensure that the family has a reasonable understanding of the disease and this involves careful review of the natural history and treatment options. I reiterate that idiopathic thrombocytopenic purpura is a benign, although alarming, condition and that serious internal haemorrhage is extremely rare and, in my experience, usually seen in the child with haemorrhagic symptoms at onset. It is good if parents can avoid an obsession, often I am afraid iatrogenic, with the significance of minor variations in the platelet count. I emphasise that treatment should be directed at the patient rather than the platelet count, and that frequent blood tests are best avoided. It is also useful to discuss the risk of bleeding in relation to platelet count and to point out that this risk, because of good platelet function,[14] is low in idiopathic thrombocytopenic purpura. I explain that the natural history of idiopathic thrombocytopenic purpura is such that patients may improve spontaneously even after years and that any form of treatment is symptomatic rather than curative. Given this low mortality and spontaneous remission a careful analysis of risk and benefits of treatment is essential.

Most parents and children who have experienced long term treatment with steroids are only too aware of the side effects and anxious to avoid them at all costs. Such treatment has no place in the management of chronic idiopathic thrombocytopenic purpura. Periodic infusions of immunoglobulin have been proposed in the responsive child, as a long term treatment but there is no justification for their routine use.[15 16] Most children need no specific treatment but should avoid aspirin and bodily contact sports. I would recommend short term steroids or immunoglobulin infusions only in the event of overt bleeding or in preparation for surgery. Other forms of treatment, such as vincristine and immunosuppressive drugs, have had their proponents, usually as treatment for symptomatic patients who have not responded to splenectomy, and the reader is referred to an excellent review by Buchanan for an analysis of their lack of benefit.[17] I have no personal experience of any of these measures except in a very few children whose thrombocytopenia is part of a more generalised autoimmune disorder. They have no place in the management of chronic idiopathic thrombocytopenic purpura. Recent reports suggest that danazol, an attenuated androgen, may benefit some patients but further studies are needed.[18]

What then are the indications for splenectomy, the earliest and most established form of treatment for chronic idiopathic thrombocytopenic purpura? It is unfortunate for paediatric practice that splenectomy is regarded by haematologists as a treatment of choice in adults with chronic idiopathic thrombocytopenic purpura refractory to steroids.[19] This thinking has in the past lead to many referrals for consideration of splenectomy if a child has not remitted within six months. In view of the mild symptoms of most patients and the significant and indefinite risk of sepsis with pneumococcus and *Haemophilus influenzae*,[20] a decision to recommend splenectomy should only be undertaken after very serious consideration. The risk of postsplenectomy sepsis is in most patients greater than the risk of serious bleeding.

While splenectomy, by removing a major source of synthesis of antibody and an important site of platelet destruction,[19] does result in an improved count in many patients it does not cure the underlying problem. It has been estimated that half of the children with idiopathic thrombocytopenic purpura will achieve normal counts after splenectomy[17] but this clearly depends on the indications. I recommend it very rarely, usually in the older child with repeated episodes of haemorrhage for which there is no local cause. While it seems that children who in the past have had a prompt response to steroids or intravenous immunoglobulin are those most likely to have sustained improvement, the response is not always predictable and it is important to explain that splenectomy usually produces at least a modest improvement in symptoms but that this is not invariable. Preoperative pneumoccal vaccine and postoperative penicillin are recommended. A review of the literature would suggest that the risk of sepsis after splenectomy may actually be greater than that of intracranial haemorrhage,[17] so the decision requires great thought.

Perhaps the most important factor in dealing with the child with idiopathic thrombocytopenic purpura is the attitude of the physician. He must listen to the very real anxieties and explain in understandable terms the risks and benefits of treatment. With this support most children with chronic idiopathic thrombocytopenic purpura can be managed without specific treatment until their disease undergoes spontaneous remission.

References

[1] McClure PD. Idiopathic thrombocytopenic purpura in children. *Am J Dis Child* 1977;**131:**357–9.

[2] Zuelzer WW, Lusher JM. Childhood idiopathic thrombocytopenic purpura. *Am J Dis Child* 1977;**131:**360–2.

[3] Imbach P, Barandun S, d'Apuzzo V, *et al.* High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;**i:**1228–31.

[4] Imbach P, Wagner HP, Berchtold W, *et al.* Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;**ii:**464–8.

[5] Krivit W, Tate D, White JG, Robison LL. Idiopathic thrombocytopenic purpura and intracranial haemorrhage. *Pediatrics* 1981;**67:**570–1.

[6] Ekert H. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;**ii:**1310.

[7] Lever AML, Brown D, Webster ADB, Thomas HC. Non-A, non-B hepatitis occurring in agammaglobulinaemic patients after intravenous immunoglobulin. *Lancet* 1984;**ii:**1062–4.

[8] Stuart MJ, Kelton JG. The platelet: quantitative and qualitative abnormalities. In: Nathan DG, Oski FA, eds. *Hematology of infancy and childhood.* Philadelphia: WB Saunders, 1987; 1343–463.

[9] Alter BP. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of infancy and childhood.* Philadelphia: WB Saunders, 1987:159–241.

[10] Harrington WJ. Are platelet-antibody tests worthwhile? *N Engl J Med* 1987;**316:**211–2.

[11] McIntosh S, Johnson C, Hartigan P, Baumgarten A, Dwyer JM. Immunoregulatory abnormalities in children with thrombocytopenic purpura. *J Pediatr* 1981;**99:**525–30.

[12] Ramos ME, Newman AJ, Gross S. Chronic thrombocytopenia in childhood. *J Pediatr* 1978;**92:**584–6.

[13] Walker RW, Walker W. Idiopathic thrombocytopenia, initial illness and long term follow up. *Arch Dis Child* 1984;**59:**316–22.

[14] Harker LA, Slitcher SJ. The bleeding time as a screening test for evaluation of platelet function. *N Engl J Med* 1972;**287:**155–9.

[15] Bussel JB, Kimberley RP, Inman RD, *et al.* Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. *Blood* 1983;**62:**480–6.

[16] Bussell JB, Schulman I, Hilgartner MW, Barandum S. Intravenous use of gammaglobulin in the treatment of chronic immune thrombocytopenic purpura as a means to defer splenectomy. *J Pediatr* 1983;**103:**651–4.

[17] Buchanan GR. The nontreatment of childhood idiopathic thrombocytopenic purpura. *Eur J Pediatr* 1987;**146:**107–12.

[18] Weinblatt ME, Kochen J, Ortega J. Danazol for children with immune thrombocytopenic purpura. *Am J Dis Child* 1988;**142:** 1317–9.

[19] McMillan R. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 1981;**304:**1135–47.

[20] Anonymous. Splenectomy—a long-term risk of infection. *Lancet* 1985;**ii:**928–9.

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Contemporary history

Paediatrics at King's College Hospital 50 years ago

PHILIP EVANS

King's College Hospital pioneered British paediatrics. It was the first teaching hospital to have a children's department, which was founded when George Frederic Still was invited to join the consultant staff in 1899. Still was himself a pioneer, being the first doctor to practise full time paediatrics as a separate specialty from adult general medicine. In 1906 he became the first professor of paediatrics.

Mind you, he was on his own. There were no clinical departments as we understand them. Now the nucleus of a department is an office, a secretary, and a telephone, with academics attached to the cell membrane. When I came here a generation after Still's arrival the department consisted of a ward and three outpatient clinics. The consultant had a coat hook, the half time registrar had a locker, and the house physician was shared with neurology—an appointment known as 'kids and nerves'.

Still had held the formative post of medical registrar and pathologist at the Hospital for Sick Children, Great Ormond Street. Some years later he was allowed to have an assistant physician, so the then incumbent of the post at Great Ormond Street, RS Frew, was appointed. Sixteen years later he retired to look after his private practice: remember that voluntary hospital consultants were not paid for their hospital work before 1948. When Frew left, Still simply arranged for the contemporary registrar from Great Ormond Street, Wilfrid Sheldon, to move to King's. Sheldon was 26 years old.

Sir Frederic Still retired in 1933. He had two wards—Pantia Ralli and Princess Elizabeth (Still was Princess Elizabeth's paediatrician; I don't know whether the Queen remembers her first doctor). When Still left, Pantia Ralli was taken away from young Sheldon and turned over to the psychiatrists. Sheldon went on alone for six years until I was appointed assistant in 1939.

Perhaps I should explain how I came to be here at all. In 1935 there was a vacancy for a medical registrar and pathologist at Great Ormond Street. George Newns and I applied, and he was appointed. I knew he was registrar at King's so I telephoned for an appointment with Sheldon, went to see him in his rooms in Upper Wimpole Street, and said that I should like to apply for the forthcoming appointment.

Wilfrid Sheldon had an unnerving habit of not speaking until he was ready. A long Sheldonian silence ensued and then he said 'Very well, I will tell them not to advertise. Start on October the first'. You see how opportunism sometimes pays.

It was a half time job that paid £70 a year, but Sheldon got me to conduct two of his rheumatism clinics (one at King's and one at Walthamstow), and with charity tea parties and so on got me a small stipend to do research into juvenile rheumatism. At that time rheumatic fever and chorea were great scourges. The London County Council maintained two and a half large hospitals solely for children with rheumatic heart disease who were treated by bed rest for months or even years. With these payments, together with fees from tutoring and correcting papers for the London Correspondence College at three pence a question, I earned about £450 a year—a living wage.

My duties were to be in outpatients twice a week, and to do business rounds with the house physician, and twice weekly teaching rounds with the chief. These teaching rounds were processional: first went the chief with the house physician and sister, followed by a nurse wheeling a trolley with instruments and notes, then the students followed by the registrar (who did not speak unless spoken to) and, finally, a junior nurse whose job it was to go to any child who cried and whisk if off to the sluice room where the cries could not be heard. After 1948–50 it was thought repressive to insist on silence, and the peace of the ward round was destroyed for ever.

I travelled daily from Pimlico to Denmark Hill by tram, which meant that I arrived for Friday's round having read the latest *Lancet,* which Dr Sheldon (driving himself in his Wolseley) had not done. One up to me, sometimes.

Rheumatic fever and chorea accounted for one third of our patients. Apart from sodium salicylate for arthritis—very effective—bed rest was the mainstay of treatment, the aim being to rest the heart and limit its injury. We now know that lying flat is not the best way to rest the heart, but it may not have been totally stupid. I knew of a child in New York (where they were allowed to sit up on bed pans) who died while straining at stool.

Tuberculosis was not the pest that it had been in the 19th century but it was still common. Scurvy had almost disappeared, but rickets was often seen. Urinary tract infections were treated by making the urine alkaline with potassium citrate. Pneumonia was common, but was fortunately more benign in children than in adults. It was treated by good nursing alone until the introduction of sulphapyridine in 1938–9, but there was no antibiotic until penicillin became available in limited quantities after the war. Dr Sheldon did not always treat mild pneumonia with sulphapyridine, as he thought that it often made the children more ill than the pneumonia did.

Gastroenteritis was treated by modified feeding. In 1934 it was discovered that babies' veins could be used for drips, but each one required a cut down for the insertion of a Bateman needle or cannula. Treatment was empirical; blood electrolyte concentrations could not be measured.

The Ramstedt operation for pyloric stenosis cured a lot of babies, but the mortality was between 4 and 20%—mostly from gastroenteritis. This was the result of the babies being nursed in an open ward with no cubicles. We could not prevent gastroenteritis from spreading and yet could barrier nurse patients with typhoid with confidence. Patients with poliomyelitis were not isolated and yet the disease did not spread throughout the hospital, probably because of 'herd' immunity. Paracentesis of the ear drum was the commonest operation carried out, but tonsillectomy and circumcision were also widely practised. In season, there were usually a couple of empyemas being drained.

That was the 1930s—time to move to the 1940s. In 1939 war broke out and because heavy bombing was expected in London the hospitals were moved out. King's was transferred to Horton Mental Hospital at Epsom, but because of evacuation of children to the country the children's department (at least the doctors, sisters, and students) went to Cuckfield in Sussex where the workhouse had a modern hospital block, though it was not well equipped to start with. There was only one hypodermic syringe, which was the property of the senior nurse; when she was sacked she took it with her. After some weeks radiographic equipment was installed in the gasman's workshop. Pathology specimens were sent by post to a mental hospital 30 miles away, so we did not get many urgent tests done. Most of what we sent was throat swabs for the diagnosis of diphtheria until we got our own laboratory about a year later. This was converted from a ward that was freed when huts were built in the grounds to take the place of wards. There were no resident doctors, but there were lodgings in the nearby village.

The summer of 1940 was beautiful and we used to pause in our tennis to watch the Battle of Britain, though we did not appreciate what was happening until it was over. One morning I was teaching with my back to the window, when I thought I was losing the attention of the audience. I droned on, and when the session was over the students told me that they had been watching a 'dog fight' in the air. One plane was shot down. The local builder jumped in his car, drove to the site, and took the German pilot prisoner.

So rural life continued; we were busy but not too busy, and patients were treated and medical and nursing students taught.

When the department moved again in 1943 because the Canadian army wanted Cuckfield Hospital I was abroad. The next location of the King's paediatric unit was at Elfinsward, Haywards Heath, which was a diocesan home for retired clergymen. I don't know what became of them, but people were always being displaced during the war.

When the war ended in 1945 King's returned to Denmark Hill, and by the time I got home in 1946 it was much as it had been before. I was assistant physician with two outpatient days and four beds, and no prospect of more until I was at least 52 years old because Wilfrid Sheldon was only eight years older than me. I was therefore tempted by an invitation to go and work at Guy's Hospital, where I would have an office and a desk and a telephone, and the promise of a secretary. What was more, the medical school would pay my salary. My income from my first three months in practice had been three guineas. The war saved me financially, as I got £650 a year in the Emergency Medical Service.

After I left Wilfrid Sheldon went on without an assistant for 18 months until the Governors appointed Dr Mary Wilmers a week or two before the National Health Service came into being in 1948, so she ushered in the new era.

Since then the department has gone from strength to strength, and the face of paediatrics has changed for the better. Sydenham's chorea inexplicably disappeared in 1939, as Wilfrid Sheldon was the first to point out in a letter to the *Lancet*. Sulphonamides, and later penicillin, were probably responsible for reducing the incidence of rheumatic fever. Post-streptococcal nephritis disappeared later, but it was already attenuated except where the original New York strain persisted, as it did in Romania. Streptococcal cross infection in hospitals gave way to staphylococcal, and then *Pseudomonas* spp came in. The 'acute mastoid', so much feared, was not seen after the early 1940s.

Tuberculosis in children was ameliorated by better living conditions, and later by BCG vaccination, but it was more accurate diagnosis and treatment with streptomycin for adults that wiped it out in many communities.

This reduction in the incidence of infectious diseases freed medical attention to concentrate on hitherto intractable diseases such as liver and kidney failure, leukaemia, congenital heart disease, and the problems associated with gross prematurity.

Just think—it is 40 years since I saw a baby with congenital syphilis!

This article is based on the address given at King's College Hospital on 1 October 1988 to mark the retirement of Sir Eric Stroud from the Chair of Child Health.

Todd Ward at King's College Hospital in the 1930s.

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Current topic

Paediatric infectious diseases: some recent advances and future priorities

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Infectious diseases present an ever changing panorama. While change and advance are not synonymous, changes in human behaviour—by presenting urgent new dilemmas—may lead to advances in understanding of disease and its transmission. The first decade of awareness of the illness now known to be due to the human immunodeficiency virus (HIV) will have been remarkable in this respect. Some of the advances in childhood infectious illness that have also occurred in the last 10 years or so together with some future priorities, inevitably personal ones, will be reviewed here.

Some recent advances

'NEW' INFECTIOUS ILLNESSES

Most are diseases known to paediatricians for many years that have been linked to a causal infecting organism for the first time. Others appear to be new illnesses, or at least recently recognised as occurring in children as well as adults. They are listed in the table. It is possible to consider only some of them further.

Table *Infections illnesses*

Illness	*Newly recognised infecting organisms*
Long recognised:	
Cat-scratch disease	Pleomorphic Gram negative bacillus[1] (not yet named)
Erythema infectiosum (fifth disease) Aplastic crisis Fetal hydrops	Parvovirus B19[2 3]
Haemolytic uraemic syndrome and haemorrhagic colitis	Enterohaemorrhagic *Escherichia coli* 0157:H7[4]
Infectious diarrhoea	Adenovirus,[5] *Aeromonas hydrophila,*[6] *Campylobacter* spp,[5] *Cryptosporidium* spp,[5] *Yersinia enterocolitica*[15]
Respiratory tract infection	*Legionella pneumophila*[7] *Chlamydia trachomatis*[8] *C psittaci* (TWAR strain)[9 10]
Roseola infantum (exanthem subitum)	Human herpesvirus-6[11]
Newly recognised in children:	
Acquired immunodeficiency syndrome[12]	Human immunodeficiency virus (HIV)
Infant botulism[13 14]	(*Clostridium botulinum*) *C barati, C butyricum*
Lyme disease[15]	*Borrelia burgdorferi*
Toxic shock syndrome[16]	*Staphylococcus aureus* exotoxin (TSST-1)

Haemolytic uraemic syndrome

In addition to the now well known enteropathogenic, enterotoxigenic, and enteroinvasive strains of *Escherichia coli,* an enterohaemorrhagic variety has been reported, which produces cytotoxins.[4] These are known either as Shiga like toxins, being very similar to that produced by *Shigella dysenteriae* type 1, or as verotoxins, Vero cells being used to detect their cytotoxic nature. A particular serotype of one of them, 0157:H7, seems likely to prove an important aetiological agent for both haemolytic uraemic syndrome (a triad of haemolytic anaemia, thrombocytopenia, and acute renal failure), in which the Shiga like toxin may cause the initial endothelial damage, and haemorrhagic colitis.[17] The recent occurrence of the haemolytic uraemic syndrome and variants of thrombotic thrombocytopenic purpura in three siblings[18] supports the suggestion[17] that the latter should also be included.

Respiratory tract infections

Chlamydial infections have been of more importance to children in the past decade than those due to *Legionella pneumophila.* Respiratory infections in young infants associated with maternally transmitted *Chlamydia trachomatis* were first described a little over 10 years ago,[8] and although chlamydial cervicitis and urethritis are now the commonest sexually transmitted infections in the United Kingdom, chlamydial pneumonitis is almost certainly underdiagnosed in young infants. Perhaps a few such cases are associated with sudden unexpected infant deaths.

In the last few years outbreaks of pneumonia have been reported in adolescents and young adults due to a strain of *Chlamydia psittaci* known as TWAR (TW for Taiwan where it was first isolated, AR for acute respiratory).[9] It seems as if this particular infection has a human spread, rather than the avian to human one of psittacosis. It may turn out to be relatively common, resembling infections associated with *Mycoplasma pneumoniae.*[10]

The acquired immunodeficiency syndrome (AIDS)

This has received more attention in the past few years than any other infection. Criteria for its diagnosis, that of the AIDS related complex in children,[19] and for diagnosis of perinatal transmission[20] have been drawn up. The number of those 14 years or less with AIDS in the United Kingdom at the end of 1987 was still very small (n=19), maternal transmission appearing likely in over two thirds.[21] Over 10 times as many children were HIV positive, one third of whom were haemophiliacs or other recipients of blood or blood components. In the AIDS cases pneumonia was the commonest presenting diagnosis, followed by encephalopathy. The number of HIV antibody positive women 15 years and older—the mothers of today and tomorrow—is, however, increasing fast. They constitute one 10th of all such cases in the United Kingdom, and one quarter of them are in Scotland.[21] A report from the European Collaborative Study of 271 children born to HIV infected mothers in eight European centres recorded a 24% transmission rate, but cautioned this was likely to be an underestimate, as follow up was still short.[22]

Lyme disease

Erythema migrans with other complications after a tick bite was recognised in parts of Europe in the first half of the century. But a small New England town—Lyme—has now given its name to this illness. Astute physicians realised that rather too many children living near each other there were being diagnosed as suffering from 'juvenile rheumatoid arthritis'.[23] Eventually a newly discovered spirochaete, *Borrelia burgdorferi,* was incriminated as causing their illness.[15] Ticks of the *Ixodes* spp were the likely vectors. After the tick bite, and the often resulting migrating erythema, central nervous system signs such as lower motor neurone facial palsies, with cerebrospinal fluid pleocytosis, and recurring arthralgia may complete the picture. The illness sometimes follows a prolonged course. Its recognition in children in this country was first reported from Southampton.[24] [25] The deer of the nearby New Forest were accused of harbouring the infected ticks; it is now known that dogs and cats living in regions where the disease is endemic may also carry the ticks.

Toxic shock syndrome

Though usually thought of as a disease confined to women using tampons, it may occur in younger children.[16] It is important for paediatricians to keep this syndrome in mind for the accompanying hypotensive shock is its most dangerous feature. Restoration of circulating blood volume is urgently needed and careful monitoring of arterial and central venous pressure.[26] Blood cultures are usually negative, but the syndrome is caused by a particular exotoxin of *Staphylococcus aureus,* called TSST-1.

ADVANCES IN UNDERSTANDING OF HOST DEFENCE

The rare inherited defects and childhood immunodeficiency disorders—of which most of us see very few examples in our professional lifetimes—have given immunologists the opportunities for making rapid advances in understanding host defence. An appreciation of how the component parts integrate to form the whole has accelerated in the past 10 years. Most of us have great difficulty in interpreting these advances, and struggle with often changing nomenclature and articles written in language we find difficult or impossible to understand. It may be helpful to summarise, in barest outline, the most fundamental aspects.

Humoral immunity depends on the ability of the short lived polymorphonuclear neutrophils to engulf bacteria and kill them with the help of the multienzyme complement cascade. It also depends on antibodies produced by B lymphocytes (which mature in fetal liver and bone marrow) and acute phase reactants such as C reactive protein.[27] The neutrophil's central role depends on five important stages—activation, deformation, chemotaxis, phagocytosis, and the killing process—the individual parts of each now almost entirely understood.[28] Complement and antibody are crucial for fully effective neutrophil function. The complement system may be triggered via antibody through its classical pathway, or through its alternative pathway directly by the infecting organism.

Cell mediated immunity relies on the longer lived macrophages (also phagocytic), which are best able to cope with the few bacterial species, and with viruses and protozoa, which live within host cells; on lymphokines (products of activated lymphocytes which include the interferons, interleukins, colony stimulating factor, and tumour necrosis factor); and on T (thymus maturing) lymphocytes.[27]

The immune system cannot know in advance what it is going to meet. Thus antigen receptors (antibodies) of a wide variety have developed on the surfaces of B lymphocytes in order to deal with the potentially very large number of foreign antigens, only one receptor being expressed on each cell. When antigen binds with its complementary receptor antibody, the cell becomes activated, there is clonal proliferation and maturation to antibody forming plasma cells, so that large concentrations of the antibody can be produced. Some of the activated B lymphocytes become non-dividing memory cells, and it is these which will be able to mount the faster and more effective secondary immune response should the orginal antigen be met again in the future.[27]

T cells, more concerned with the control of intracellular infection, also, like B lymphocytes, have their individual but structurally different antigen receptors that have the ability to recognise antigen and produce memory cells. There are two main subsets of T cells, the helper/inducer cells (CD4, CD standing for clusters of differentiation, previously T4), and the cytotoxic/suppressor cells (CD8, previously T8). T helper cells recognise cell surface antigens in association with molecules of the class II major histocompatibility complex, and release gamma interferon to activate macrophages. The cytotoxic T cells are concerned with class I major histocompatibility complex on the surface of cells infected by virus, which can kill the virally infected cells before they replicate.[27]

Antibody formation by B lymphocytes needs the collaboration of the CD4 cells. It is the latter that are the primary target of the HIV; as they are lost progressively, so the ability to secrete antibodies is lost. The activity of suppressor T cells is uppermost in the newborn infant, and presumably through most of fetal life.[29] Thus there is a suppression of B cell differentiation to B cells and antibody production. The newborn infant also has deficiencies of complement and of certain antibodies—both exaggerated by preterm birth—so that his neutrophil response is less than efficient. Activation is poor, so there is little increase in surface receptors on the cell, and less ability to stick. The cells are unusually rigid, so their ability to adhere to surfaces or move through vascular endothelium to the site of infection is compromised, and hence chemotaxis is slower. Phagocytosis, the ability to engulf micro-organisms, may be normal in otherwise healthy infants, but in stressed or infected infants it is less effective. And the relative lack of enzymes needed for the respiratory burst that generates toxic oxygen radicals such as superoxide and hydrogen peroxide may lead to defective killing.[30] Further, if experimental work is relevant to the human, bone marrow reserves may be easily exhausted so that the infected infant becomes neutropenic.[31]

ADVANCES IN LABORATORY DIAGNOSIS

Tests for antibody such as the enzyme linked immunoadsorbent assay (ELISA), for antigen such as latex agglutination, and for endotoxin such as the limulus lysate test, have been more widely applied in recent years. The first two may be very useful for quick confirmation of the diagnosis when a certain micro-organism is suspected. Then the acute phase reactant C reactive protein—first found in the serum of patients with pneumonia in the 1930s—has attracted renewed interest recently, with greatly improved and reasonably rapid quantitative methods available for its detection. Its greatest use may be in following the course of an infection rather than in early diagnosis.

But it is in molecular biology that we have not only one of the fastest growing areas in medicine but one which, when it has realised its full potential, will be of enormous benefit in the field of infectious diseases.[32] Techniques such as monoclonal antibody production (commercially exploited to make large amounts of specific antibody available), protein biochemistry, and recombinant DNA technology probably benefit diagnosis more than treatment at present. The characterisation of bacterial DNA and proteins has meant simpler ways of typing organisms. Plasmid DNA isolation, and the recognition of specific sequences of DNA with DNA probes, are being used in clinical microbiology, often elucidating the epidemiology of outbreaks of infection.[33]

Routine microbiology laboratories in many hospitals may not be able to offer all these services but will know where they are available. Clinicians need therefore to be aware of what is possible, and to keep in close touch with their microbiologist colleagues. Talking over clinical problems with them, and ensuring they get the fullest information possible about patients' illnesses, will bring its rewards.

ADVANCES IN TREATMENT

Antiviral drugs

The two which seem to have emerged as potentially the most promising where childhood infections are concerned are acyclovir and ribavirin. Ganciclovir still needs further evaluation. Acylovir will be most useful for treatment of herpes simplex virus infections either in the neonatal period (where vidarabine is another possibility), or in the immunocompromised child for whom it may also be needed for varicella zoster infections.

Respiratory illness is the main reason for hospital admission in children under 5 years of age, and the major cause of it is respiratory syncytial virus. The organism is also frequently responsible for hospital cross infection. While deaths in otherwise healthy infants are now very unusual, respiratory syncytial virus infections may have a fatal outcome in infants with congenital heart disease, especially when accompanied by pulmonary hypertension, and in immunocompromised children. Ribavirin is particularly active against RNA viruses—especially respiratory syncytial virus and parainfluenza. A case can be made for the use of aerosol ribavirin in immunocompromised children and those with congenital heart disease and bronchopulmonary dysplasia if they have proved infection with either of those two organisms. But large multicentre trials are surely justified before this very expensive drug is used on a large scale,[34 35] as previous trials have involved relatively small numbers only.

ORAL REHYDRATION THERAPY FOR DIARRHOEA

This is an important advance which has been responsible for the yearly saving of half a million childrens' lives. Ebrahim points out that despite this, it is still used by a minority of the population in developing countries.[36] Even in the United States there are an average of 500 deaths yearly from diarrhoea; and the oral glucose electrolyte solutions are frequently not prescribed by paediatricians there, nor used by parents.[37] The same may be true in this country.

INTRAVENOUS IMMUNOGLOBULIN

The results of trials of intravenous immunoglobulin in children with AIDS, and with mucocutaneous lymph node syndrome (Kawasaki disease) have been favourably reviewed.[38] As a causal organism of this latter supposedly infectious illness is still unidentified, this treatment must be regarded as empirical. Small trials of the use of immunoglobulin (intravenous and intramuscular) have also been carried out in the neonatal period, either as a therapeutic measure in infants with suspected or later proved bacterial infection, or both,[39] or as a preventive measure in preterm and low birthweight infants.[40 41] These trials have suggested some benefit for its use, as has one trial using an IgM enriched intravenous preparations.[42] These studies are careful and important contributions, but large scale multicentre trials are necessary. The preparations need to be refined to be of most benefit against likely infecting organisms causing neonatal infection; the duration of their beneficial effects needs to be worked out, and it is important to be certain they will not interfere with normal responses to routine immunisations. The development of non-A non-B hepatitis in adult trials of intravenous immunoglobulin has been reported, but should be avoidable. Long term safety needs to be ensured before the immunoglobulins are used on a wide scale in neonatal units. These preparations, however, are more easily available than granulocytes for transfusion, which have also undergone small controlled trials, but similarly need large multicentre ones.[43] If both forms of treatment were proved safe in the short and long term, a combination of the two might be more logical on immunological grounds.

ADVANCES IN PREVENTION

The eradication of smallpox in 1979 must surely be recognised as an outstanding achievement by the World Health Organisation (WHO). Enormous credit is due to those responsible for the planning and implementation of what must have seemed an almost insuperable task.

Serious *Haemophilus influenzae* type b infections affect one in 200 American children in the first five years of life,[44] and their prevalence in this country is rising. The organism is one of the preschool child's most dangerous pathogens. A capsular polysaccharide (polyribosyl-ribitol-phosphate) vaccine was licensed for use in the United States in 1985 after trials. Although it will not protect the youngest children (antibody responses are poor until about 18 months of age), and will have no impact on non-typable strains which account for a sizeable proportion of upper respiratory tract infections,[44] it has been assessed as being cost effective.[45] Further trials, with other vaccines aimed at protecting younger infants, are being carried out in several countries.

Hepatitis B vaccine is to some extent unique in that if it could be given to all infants born to women carrying the hepatitis B surface antigen, not only is there the prospect of preventing chronic hepatitis, but, perhaps, hepatocellular carcinoma as well.

Some future priorities

IMMUNISATION

Universal childhood immunisation is one of the four priorities selected by the United Nations Children's Fund (Unicef) in collaboration with the WHO in their drive to improve the health and nutrition of the world's children. The Director General of WHO has been reported as saying that in 1987 just half of the latter were now receiving immunisation against poliomyelitis, diphtheria, pertussis, tetanus, measles, and tuberculosis; the expanded programme was judged to be preventing more than one million deaths from measles, neonatal tetanus, and pertussis, and more than 175 000 cases of poliomyelitis. But the goal of health for all by the year 2000 still faces enormous difficulties in the poverty stricken parts of the world.

The United Kingdom certainly has its own house to put in order too. Given that uptake of immunisation is least in urban areas,[46] primary health care teams there need to know that it is primarily *their* informed attitudes and enthusiasm, backed by efficient organisation, which lead to the desired high uptake.[47] It is easy to blame non-compliance or non-completion of schedules on socioeconomic factors, but this is probably unjustifiable.[48] There is no reason for health professionals in this country not to be well informed about the very few contraindications to immunisation existing. Copies of the recently distributed green book[49] need to be in every health clinic, and on the desks of general practitioners and paediatricians. The information is clearly set out, should allow those responsible to speak with one voice, and prevent confidence being undermined by the wide coverage given to every pronouncement of the anti-immunisation lobby. The new measles, mumps, and rubella vaccine introduced in October 1988 needs a 95% uptake to eradicate these rarely (at least in this country) lethal, but occasionally very disabling infections. A spirit of healthy competition between districts to achieve such levels for *all* immunisations in children would not go amiss.

PREVENTION OF CHORIOAMNIONITIS ASSOCIATED PRETERM BIRTH

It may seem out of place to discuss this primarily maternal infection here, but I think paediatricians will have to take the lead in urging obstetricians to take chorioamnionitis more seriously. This inflammation of the decidua, fetal membranes, and umbilical cord is mostly clinically silent. It is only diagnosed by pathologists if they decide to look for it and if they receive the placenta in the first place. But it is at its most prevalent at low gestations, and there is increasing suspicion that it is a cause rather than a sequel to premature rupture of the membranes in many cases.[50] The most common infecting organism may well turn out to be *Ureaplasma urealyticum*.[51] This is an organism of low virulence (except as we have learned recently for very immature babies[52]), and it can flourish in amniotic fluid for several weeks. Certain bacteria, of which the ureaplasmas are prime examples, produce phospholipase A_2, an enzyme necessary for the formation of arachidonic acid. This in turn is a substrate for prostaglandin synthesis, and prostaglandin is involved in the initiation of labour.[50] Epidemiological surveys to discover precisely who is at risk, and large multicentre trials of possible treatments, are badly needed. Time spend on chorioamnionitis might ultimately prove very rewarding. Many surviving infants of extremely low birth weight have required weeks of intensive care, and later outcome is not always the unqualified success story many would have us believe. If the babies could stay inside the uterus *safely* for longer, they, their parents, and their nurses and doctors would surely be grateful.

URINARY TRACT INFECTION

It goes without saying that earlier diagnosis would do much to improve results. About half the children receiving dialysis for renal failure are in this unenviable situation because their renal failure is secondary to scarring and chronic atrophic pyelonephritis. Such involvement of the renal parenchyma is also an important cause of hypertension. The infections which will lead to these end results are usually acquired in infancy or well before 5 years of age, when reflux is present. Each child that is hypertensive or dialysed for this reason must represent a failure of early diagnosis, or of effective treatment, or of failure to prevent recurrence, relapse, or reinfection. The younger the child, the more non-specific are symptoms of urinary tract infection likely to be, and no clinical examination of such infants can be complete without urinalysis and culture of a satisfactorily collected and processed specimen. If this really fundamental component of good medicine was conscientiously practiced, if all children with diagnosed urinary tract infection were properly investigated, treated, and kept under long term surveillance, much subsequent illness and disruption of family life could be avoided.[53]

HEALTH EDUCATION

Sexually transmitted diseases started to rise steeply in frequency from the 1960s; this was partly due to improved diagnosis. Promiscuous sex from an early age may lead to carcinoma of the cervix, impaired fertility, or be the cause of sometimes disabling, occasionally lethal infections in infants born to mothers infected with certain sexually transmitted organisms. The suggestion of Curtis and colleagues that sex education should be taken very much more seriously is surely important,[54] and this difficult and sensitive task may need the involvement of paediatricians.

CONTROL OF INFECTION

In his review of treatment of diarrhoeal diseases in developing countries, Ebrahim pointed out that education about washing the hands can lead to an 85% reduction of secondary attack rates of diarrhoea within families.[36] With an increasing population of preschool children at nurseries and play groups in this country such education is also of profound importance for staff working there, and by example for the children. It is not only gastrointestinal pathogens that may be transmitted via the hands, but certain respiratory tract pathogens as well. In hospital too, effective hand washing conscientiously practised by all staff would do much to reduce the very considerable burden of nosocomial infection there. The increasing numbers of infections with *Salmonella* spp and with *Listeria monocytogenes* now occurring are likely to be of serious importance to newborn infants and immunocompromised older children. An asymptomatic and unsuspected carrier mother may transfer salmonella to her newborn infant. He or she is then frequently the index case for neonatal unit epidemics. While the mother with listeriosis is more likely to be febrile and have some malaise as a warning, this is not invariable. Only effective infection control measures will prevent these epidemics occurring.

There is an urgent need for more paediatricians to make infectious diseases a special interest. The subject will always be of special importance for children. The possibilities for accurate diagnosis and effective treatment, and the opportunities for prevention, have never been greater.

References

[1] English CK, Wear DJ, Margileth AM, Lissner CR, Walsh GP. Cat-scratch disease. Isolation and culture of the bacterial agent. *JAMA* 1988;**259:**1347–52.

[2] Anderson MJ, Lewis E, Kidd IM, Hall SM, Cohen BJ. An outbreak of erythema infectiosum associated with human parvovirus infection. *J Hyg (Camb)* 1984;**93:**85–93.

[3] Anderson LJ. Role of parvovirus B19 in human disease. *Pediatr Infect Dis J* 1987;**6:**711–8.

[4] Sack RB. Enterohemorrhagic Escherichia coli. *N Engl J Med* 1987;**317:**1535–7.

[5] Manuel PD, Walker-Smith JA, Tomkins A. *Infections of the gastrointestinal tract.* Edinburgh: Churchill Livingstone, 1986.

[6] Figueroa G, Galeno H, Soto V, Troncoso M, Hinrichsen V, Yudelevica A. Enteropathogenicity of Aeromonas species isolated from infants: a cohort study. *J Infect* 1988;**17:**205–13.

[7] Muldoon RL, Jaecker DL, Keifer HK. Legionnaires' disease in children. *Pediatrics* 1981;**67:**329–32.

[8] Beem MO, Saxon EM. Respiratory-tract colonization and a distinctive pneumonia syndrome in infants infected with Chlamydia trachomatis. *N Engl J Med* 1977;**296:**306–10.

[9] Grayston JT, Kuo C-C, Wang S-P, Altman J. A new Chlamydia psittaci strain, TWAR, isolated in acute respiratory tract infection. *N Engl J Med* 1986;**315:**161–8.

[10] Anonymous. TWAR—Chlamydia in a new guise? *Lancet* 1988;**i:**974–5.

[11] Yamanishi K, Okuno T, Shiraki K, *et al.* Identification of human herpesvirus-6 as a causal agent for exanthem subitum. *Lancet* 1988;**i:**1065–7.

[12] Oleske J, Minnefor A, Cooper R, *et al.* Immune deficiency syndrome in children. *JAMA* 1983;**249:**2345–9.

[13] Midura TF, Arnon SS. Infant botulism: identification of Clostridium botulinum and its toxin in faeces. *Lancet* 1976;**ii:** 934–6.

[14] Arnon SS. Infant botulism: anticipating the second decade. *J Infect Dis* 1986;**154:**201–6.

[15] Steere AC, Grodzicki RL, Kornblatt AN, *et al.* The spirochetal etiology of Lyme disease. *N Engl J Med* 1983;**308:**733–40.

[16] Todd JK, Fishaut M, Kapral FA, Welch T. Toxic-shock syndrome associated with phage-group-I staphylococci. *Lancet* 1978;**ii:**1116–8.

[17] Cleary TG. Cytotoxin-producing Escherichia coli and the hemolytic uremic syndrome. *Pediatr Clin North Am* 1988;**35:** 485–501.

[18] Elias M, Horowitz J, Tal I, Kohn D, Flatau E. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome in three siblings. *Arch Dis Child* 1988;**63:**644–6.

[19] Centers for Disease Control. Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR* 1987;**36:**225–30, 235–6.

[20] Task Force on Pediatric AIDS. Perinatal human immunodeficiency virus infection. *Pediatrics* 1988;**82:**941–4.

[21] Public Health Laboratory Service AIDS Centre. Human immunodeficiency virus infection in the United Kingdom: quarterly report 2. The epidemic to 31 December 1987, with special reference to children. *J Infect* 1988;**17:**71–82.

[22] The European Collaborative Study. Mother-to-child transmission of HIV infection. *Lancet* 1988;**ii:**1039–46.

[23] Steere AC, Malawista SE, Bartenhagen NH, *et al.* The clinical spectrum and treatment of Lyme disease. *Yale J Biol Med* 1984;**57:**453–61.

[24] Williams D, Rolles CJ, White JE. Lyme disease in a Hampshire child—medical curiosity or beginning of an epidemic? *Br Med J* 1986;**292:**1560–1.

[25] Bateman DE, White JE, Elrington G, Lawton NF, Muhlemann MF, Greenwood RJ. Three further cases of Lyme disease. *Br Med J* 1987;**294:**548–9.

[26] Buchdahl R, Levin M, Wilkins B, *et al.* Toxic shock syndrome. *Arch Dis Child* 1985;**60:**563–7.

[27] Roitt I. *Essential immunology.* 6th ed. Oxford: Blackwell Scientific Publications, 1988.

[28] Malech HL, Gallin JI. Immunology. Neutrophils in human disease. *N Engl J Med* 1987;**317:**687–94.

[29] Andersson U, Britton S, de Ley M, Bird G. Evidence for the ontogenic precedence of suppressor T cell functions in the human neonate. *Eur J Immunol* 1983;**13:**6–13.

[30] Hill HR. Biochemical, structural, and functional abnormalities of polymorphonuclear leukocytes in the neonate. *Pediatr Res* 1987;**22:**375–82.

[31] Christensen RD, Macfarlane JL, Taylor NL, Hill HR, Rothstein G. Blood and marrow neutrophils during experimental group B streptococcal infection: quantification of the stem cell, proliferative, storage and circulating pools. *Pediatr Res* 1982;**16:** 549–53.

[32] Coates ARM. The impact of molecular biology on the diagnosis and treatment of infection. *J Infect* 1986;**13:**217–33.

[33] Hawkey PM. Molecular methods for the investigation of bacterial cross-infection. *J Hosp Infect* 1987;**9:**211–8.

[34] Wald ER, Dashefsky B, Green M. In re ribavirin: a case of premature adjudication? *J Pediatr* 1988;**112:**154–8.

[35] Isaacs D, Moxon ER, Harvey D, *et al.* Ribavirin in respiratory syncytial virus infection. A double blind placebo controlled trial is needed. *Arch Dis Child* 1988;**63:**986–90.

[36] Ebrahim GJ. Looking beyond oral rehydration therapy. *Br Med J* 1987;**295:**1222–3.

[37] Snyder J. Too many deaths from diarrhea. *JAMA* 1988;**260:** 3329.

[38] Stiehm ER. Human gamma globulins as therapeutic agents. *Adv Pediatr* 1988;**35:**1–72.

[39] Sidiropoulos D, Böhme U, von Muralt G, Morella A, Barandun S. Immunoglobulin-substitution bei der Behandlung der neonatalen Sepsis. *Schweiz Med Wochenschr* 1981;**111**:1649–55.

[40] Haque KN, Zaidi MH, Haque SK, Bahakim H, El-Hazmi M, El-Swailam M. Intravenous immunoglobulin for prevention of sepsis in preterm and low birth weight infants. *Pediatr Infect Dis* 1986;**5**:622–5.

[41] Conway SP, Gillies DRN, Docherty A. Neonatal infection in premature infants and use of human immunoglobulin. *Arch Dis Child* 1987;**62**:1252–6.

[42] Haque KN, Zaidi MH, Bahakim H. IgM enriched intravenous immunoglobulin therapy in neonatal sepsis. *Am J Dis Child* 1988;**142**:1293–6.

[43] Cairo MS. Granulocyte transfusions in neonates with presumed sepsis. *Pediatrics* 1987;**80**:738–40.

[44] Moxon ER. Haemophilus influenzae vaccine. *Pediatrics* 1986; **77**:258–60.

[45] Cochi SL, Broome CV, Hightower AW. Immunization of US children with Hemophilus influenzae type b polysaccharide vaccine. A cost effectiveness model of strategy assessment. *JAMA* 1985;**253**:521–9.

[46] Jarman B, Bosanquet N, Rice P, Dollimore N, Leese B. Uptake of immunisation in district health authorities in England. *Br Med J* 1988;**296**:1775–8.

[47] Polnay L. Immunisation for all? *Arch Dis Child* 1988;**63**:1507–8.

[48] Nicoll A, Jenkinson D. Decision making for routine measles/MMR and whooping cough immunisation. *Br Med J* 1988;**297**: 405–7.

[49] Department of Health and Social Security, Welsh Office and Scottish Home and Health Department. *Immunisation against infectious disease.* London: HMSO, 1988.

[50] Romero R, Mazor M, Wu YK, *et al.* Infection in the pathogenesis of preterm labor. *Semin Perinatal* 1988;**12**:262–79.

[51] Cassell GH, Waites KB, Gibbs RS, Davis JK. Role of ureaplasma urealyticum in amnionitis. *Pediatr Infect Dis* 1986;**5**: S247–52.

[52] Cassell GH, Waites KB, Crouse DT, *et al.* Association of Ureaplasma urealyticum infection of the lower respiratory tract with chronic lung disease and death in very-low-birth-weight infants. *Lancet* 1988;**ii**:240–5.

[53] Smallpeice V. *Urinary tract infection in childhood and its relevance to disease in adult life.* London: Heinemann Medical Books, 1968:133–41.

[54] Curtis HA, Tripp JH, Lawrence C, Clarke WL. Teenage relationships and sex education. *Arch Dis Child* 1988;**63**:935–41.

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Neonatology—then and now *(C H M Walker)*

Oxygen tension in the newborn (1957)

Low oxygen tension in the management of newborn infants

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(Arch Dis Child 1957;32:397–9)

This paper, which was based on a presentation read at the VIIIth International Congress of Paediatrics in Copenhagen, July 24 1956, starts with the somewhat dramatic statement:

> 'Prolonged administration of oxygen in high concentrations to premature infants is now being abandoned in most countries, thanks to the studies on retrolental fibroplasia which have shown its harmful effects on the eyes.'

Later in the introduction we find:

> 'The frequent co-existence of retrolental fibroplasia and cerebral palsy as shown in the papers by Ingram and Kerr (1954) and Klause (1955) may perhaps also justify relating cerebral palsy to oxygen therapy.'

The paper then describes 33 infants (21 term and 12 'premature') treated in atmospheres of 15% oxygen, 85% nitrogen, and in whom oxygen saturations fell by about 10 volumes %. Though this was in the early days of such studies in Lund others had exposed infants to low ambient tensions three years previously and reported that 115 mm Hg oxygen did not 'involve undue risks'. Some term infants were cyanosed to start with but then became pink with 'deep breathing, bradycardia (100–110 per min) and slight hypothermia'. The preterm babies were 'often a little cyanotic' but their attacks of cyanosis and dyspnoea were 'not more often than usual' and it was thought that they might possibly be even less frequent. They had temperatures of 33°–36°C for one or two weeks but remained in 'excellent condition'.

Today. Ever since the relationship between oxygen and retrolental fibroplasia was suspected paediatricians have been walking the tightrope between giving enough oxygen to prevent cerebral hypoxia and metabolic acidosis but less than that which is now thought to cause post hyperoxia capillary closure and retinopathy. Currently the 'hypoxaemic hypothesis' is receiving much attention and we have to accept that the pathogenesis of retinopathy is not as straightforward as it once appeared to be, especially as the very immature retina seems to be damaged even though the infants have been nursed in nothing but atmospheric air. It is likely that the various problems of the preterm baby such as respiratory irregularity and pulmonary pathology cause wide swings in oxygen pressure which stimulate retinal and cerebral vasoactivity and these fluctuations may well be as, if not more, important than the actual levels reached, high or low. Unfortunately, continuous monitoring of transcutaneous oxygen tension does not seem to lessen the incidence of retinopathy in infants under 1000 g birth weight—that is, those at greatest risk—though it may help in those over that weight.[1] It was thought that oxygen tensions below that of atmospheric air might be prophylactic but the authors had to admit that their:

> 'Material is too limited to tell whether there is a greater survival rate with this treatment or fewer cases of retrolental fibroplasia, hyaline membrane disease or cerebral palsy.'

Though it is unlikely that paediatricians today would embark on further investigations of this nature, this was a brave effort in the early days of oxygen therapy studies in the newborn.

Reference

[1] Bancalari E, Flynn J, Goldberg RN, *et al.* Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. *Pediatrics* 1987;79:663–9.

Sven Sjostedt graduated first from the University of Malmo (1929) and proceeded to Lund where he received his licenciate medical degree in 1938 and his doctorate in 1946. He became Assistant Professor in the Department of Bacteriology (1946) where he had prepared his doctorate thesis on 'Pathogenicity of certain serological types of *E Coli*'; and in 1948 was appointed Assistant Professor in the Department of Obstetrics and Gynaecology.

He moved to one of Sweden's six regional hospitals in Linkoping as Head of the Department of Obstetrics and Gynaecology, later becoming Assistant Medical Head of that hospital. Along with other hospital planning he took a major role in the development of the new University in Linkoping and is well known as a regular contributor to medical literature. He was one of the last citizens to be awarded the RNO (Knight of the Order of the Northern Star) before such honours were discontinued.

Professor Gosta Rooth (retired 1984) graduated in 1945, University of Lund. After experience in the Royal Swedish Navy and a year in pathology he joined the Department of Internal Medicine. In 1949 he initiated a lung function laboratory and soon became involved in perinatal research. He moved to Uppsala in 1973 where his wife was appointed Chairman of the Department of Ethnology and where he was appointed to a personal chair in perinatal research. He is well known for his work on acid base balance and more recently for his contributions along with Albert and Renate Huch on percutaneous gas analysis techniques. He has travelled widely to study and as visiting professor in centres in Europe, the Americas, Asia, and Australia. He has numerous publications to his credit and his book *Acid Base and Electrolyte Balance* has been translated into 10 languages. His recent books include *Roots of Perinatal Medicine* (1984) and *Perinatal Acid Base Balance* (1987). He initiated the Scandinavian Congress of Perinatal Medicine and was, at the time of writing, still Chairman of the International Federation of Gynecology and Obstetrics Standing Committee on Perinatal Mortality and Morbidity. And yet he found time to take an active part in work of his local town council! He is an honorary member of the Finnish and Italian Societies of Perinatal Medicine and was awarded the Maternity Prize of the European Society of Perinatal Medicine in 1980.

Archives of Disease in Childhood, 1989, **64,** 1341–1344

Correspondence

Neonatal urological ultrasound

Sir,

It is a cause for concern that I find the statement 'all patients underwent renography and cystography, with anatomical localisation by intravenous urography and sometimes antegrade pyelography', in a paper published in 1989.[1] The obsessive desire for full assessment should not override management based on a primary division of patients into those requiring early intervention and those requiring careful follow up. For example, dilatation of one renal tract in a neonate may resolve spontaneously without surgery. There is no single imaging pathway that is correct for all neonates with urinary abnormalities. Prudence in the use of ionising radiation dictates the need for individual assessment by surgeon and radiologist followed by the use of investigations relevant to the individual problem.

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Reference

[1] Clarke NW, Gough DCS, Cohen SJ. Neonatal urological ultrasound: diagnostic inaccuracies and pitfalls. *Arch Dis Child* 1989;**64**:578–80.

Dr Clarke comments:

While we agree that not all cases with urinary tract dilatation at birth require early surgical intervention, we maintain that in order to be sure which cases are best managed conservatively, accurate diagnosis must first be made.

Regarding the example quoted by Dr Levick, we would certainly not advocate the full investigation of a neonate with a transiently dilated urinary tract. If the dilatation persists, however, the information provided by an ultrasound scan is insufficient to provide accurate diagnosis and plan appropriate management. This fact is confirmed by the results of our paper.

We do tailor our investigations to the individual child but it is inappropriate to dispense with definite imaging as this is the only way to make specific diagnosis. To settle for anything less is to adopt a policy of 'best guess'. This is neither appropriate nor safe in current urological practice.

Sir,

In a recent paper by Clarke *et al* investigating neonatal urological scanning it was pointed out that this is not absolutely reliable and that a number of misdiagnoses might lead to major morbidity.[1] We report a case that emphasises the message.

A girl was born at full term after the antenatal scan had shown a multicystic right kidney and a normal left kidney. Postnatal scan and intravenous urography showed dilatation of the collecting system. She was referred to a regional paediatric hospital. There, ultrasound showed a right duplex system with dilatation and a large ureterocele and a dimercaptosuccinic acid (DMSA) isotope scan confirmed this finding with little function in the upper pole.

She was listed for a right upper heminephrouretectomy three months later. At operation she was found to have a Wilms' tumour occupying the right upper calices and she underwent nephrectomy. The tumour was of favourable histology and as there was no other spread she received weekly courses of vincristine only for 10 weeks.

This case confirms the view that full investigation of all antenatally detected urinary tract abnormalities must be undertaken to prevent missing cases with a potentially lethal outcome.

Reference

[1] Clarke NW, Gough DCS, Cohen SJ. Neonatal urological ultrasound: diagnostic inaccuracies and pitfalls. *Arch Dis Child* 1989;**64**:578–80.

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Sir,

Clarke *et al* are quite correct to emphasise that ultrasound alone is rarely enough to initiate treatment of renal tract abnormalities detected antenatally.[1] Their paper, however, does not define the precise role of ultrasound and underestimates its diagnostic capabilities in experienced hands.

The role of antenatal ultrasound is twofold. Firstly to detect abnormalities incompatible with a normal life expectancy so that termination of pregnancy can be offered. A recent study has shown good specificity of ultrasound in this situation.[2] Secondly to forewarn of structural renal abnormalities so that these can be investigated after birth. The specific cause for renal tract dilatation at this stage is not important.

Postnatally the situation is quite different. Ultrasound clearly shows pelvicaliceal and ureteric dilatation, bladder volume and wall thickness, the presence of diverticula and ureteroceles, and dilatation of the posterior urethra in cases of posterior urethral valves. Dilatation of collecting systems does not necessarily infer obstruction and further imaging is necessary to exclude reflux or non-obstructed dilated systems. Pelviureteric junction obstruction often has a characteristic appearance on ultrasound, however, and it is surprising that Clarke *et al* found this abnormality to be accurately diagnosed in only 14 of 35 cases. We are not told what the ultrasound diagnoses in the other 21 was, presumably dilatation of unknown cause. Cystic renal dysplasia can be accurately diagnosed by ultrasound in most cases if the strict criteria of non-communicating cystic spaces, which vary in size and number, is adhered to. It is well recognised that in a few cases it may be difficult to differentiate from hydronephrosis but this is readily achieved either by cyst puncture or radionuclide scintigraphy. It is, however, good practice in all cases to perform a dimercaptosuccinic acid (DMSA) scintigram to confirm total absence of function.

The place of postnatal renal tract ultrasound is quite clear. It should act as a guide to the next examination, although in many cases the specific diagnosis will be apparent. Tudor and Whitaker have recently described a protocol for the detection and management of the dilated fetal urinary tract, which is to be commended.[3] The ultrasound scans should be performed by individuals skilled in paediatric ultrasound. In a tertiary referral centre one would expect all the scans to be repeated by such an individual before the initiation of treatment or further investigation.

References

[1] Clarke NW, Gough DCS, Cohen SJ. *Arch Dis Child* 1989;**64:** 578–80.

[2] Arthur RJ, Irving HC, Thomas DFM, Watters JK. *Br Med J* 1989;**298:**1419–20.

[3] Tudor J, Whitaker RH. *Clin Radiol* 1989;**40:**229–30.

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Gall stones in homozygous sickle cell disease

Sir,

We recently communicated detailed findings on the prevalence and risk factors for gall stones in children with homozygous sickle cell disease.[1] The study has been repeated to include other sickle genotypes for which there are few data,[2] and this has enabled comparison of gall stone prevalence between genotypes. It has also enabled us to examine the role of haemolytic rate and mean serum bilirubin concentration, which is the prime determinant of gall stone prevalence in homozygous sickle cell disease.[1]

The children who participated in the Jamaican cohort study of sickle cell disease were aged between 6 and 14 years at the date of the study. Gall stone prevalence was determined by real time ultrasound in a cross sectional study with informed consent in every case. Details of the number of children with each genotype, the total examined, and the prevalence of gall stones are given in the table. The mean serum total bilirubin concentration for each genotype was calculated from steady state values obtained at each child's birthday after four years; this is because of the rapid change in haematological indices before this age.[3]

Table *Details of children studied*

Genotype	*No of children in cohort study*	*No of children screened*	*No (%) with gall stones*	*Mean (range) serum bilirubin (µmol/l)*
SS	242	218	30 (14)	35 (27–38)
SB°	11	9	2 (22)	27 (20–35)
SC	152	138	4 (3)	19 (16–22)
SB^{+}	33	25	0	15 (12–17)

Gall stones were more common in homozygous sickle cell (SS) than sickle cell/haemoglobin C (SC) disease ($\chi^2=9{\cdot}7$, $p<0{\cdot}01$), but other differences in prevalence were not significant. Gall stone prevalence was unreliably estimated in sickle cell/β (SB) thalassaemia due to small patient numbers. Mean serum bilirubin concentrations varied by genotype in a similar manner to gall stone prevalence, and data from the cohort study have shown differences by genotype in mean haemoglobin and reticulocyte count consistent with variation in haemolytic rate.[4] Our data indicate that haemolysis, mean bilirubin, and gall stone prevalence vary by sickle genotype, and that the risk of gall stones is low in children with SC disease and SB^{+} thalassaemia.

References

[1] Webb D K H, Darby J S, Dunn D T, Terry S I, Serjeant G R. Gall stones in homozygous sickle cell disease. *Arch Dis Child* 1989;**64:**693–6.

[2] Rennals M B, Dunne M G, Grossman N J, Schwartz A D. Cholelithiasis in patients with major sickle hemoglobinopathies. *Am J Dis Child* 1984;**138:**66–7.

[3] Serjeant G R, Grandison Y, Lowrie Y, Phillips J, Serjeant B E, Vaidya S. The development of haematological changes in homozygous sickle cell disease: a cohort study from birth to 6 years. *Br J Haematol* 1981;**48:**533–43.

[4] Stevens M C G, Maude G H, Beckford M, *et al.* Haematological change in sickle cell-haemoglobin C disease and sickle cell-beta thalassaemia: a cohort study from birth. *Br J Haematol* 1985;**60:**279–92.

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Haemophilus influenzae type b disease in the Oxford region

Sir,

Tudor-Williams *et al* report an incidence of systemic *Haemophilus influenzae* type b disease in children less than 5 years of age of 33·4/100 000.[1] This was determined from a detailed laboratory based study in the Oxford region and they urge others to set up similar prospective studies.

I have examined Hospital Activity Analysis (HAA) data for all deaths and discharges for *H influenzae* meningitis (ICD Code 320·0) and acute epiglottitis (ICD Code 464·3) in the South Western region from 1976–86 and 1979–86 respectively. These two groups accounted for 80% of all invasive *H influenzae* type b disease in those under 5 in the Oxford study. A total of 268 cases of meningitis and 118 cases of epiglottitis were identified. The annual incidence rate for *H influenzae* meningitis in children less than 5 years of age was 14·1/100 000 (compared with 23·6/100 000 in Oxford) and 8·6/100 000 for epiglottitis, similar to that found in Oxford. Over the last four years, however, the incidence rate for *H influenzae* has been 18·1/100 000, which may represent an improvement in data collection. If immunisation will prevent 85% of systemic *H influenzae* type b disease[2] the impact of such a programme will be detectable by monitoring HAA data. The Communicable Disease Centre at Colindale already collect details of invasive *H influenzae* disease. Local surveillance could also include scrutiny of statutory notifications and death registrations. It would seem that information systems already in place should be able to monitor the effectiveness of introducing immunisation for *H influenzae*.

References

[1] Tudor-Williams G, Frankland J, Isaacs D, *et al.* Haemophilus influenzae type b disease in the Oxford region. *Arch Dis Child* 1989;**64**:517–9.

[2] Eskola J, Petola H, Takala AK, *et al.* Efficacy of Haemophilus influenzae type b polysaccharide—diphtheria toxoid conjugate vaccine in infancy. *N Engl J Med* 1987;**317**:717–22.

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Effect of clonidine on serum gonadotrophin concentrations

Sir,

Clonidine, an $alpha_2$ adrenergic agonist and a potent stimulator of pituitary growth hormone release, is being used in the treatment of short children in some centres.[1] Clonidine also causes release of luteinising hormone in rats, however, and restoration of suppressed luteinising hormone pulsatility.[2 3] This observation could have important implications for the treatment of short children because clonidine might induce puberty. We report the effects of clonidine on serum gonadotrophins in normal subjects.

Clonidine (0·15 mg/m^2 orally) was given at 09.00 (time 0) to eight healthy adult men volunteers and placebo to one subject. Twelve blood samples to measure luteinising hormone and follicle stimulating hormone were drawn at 15 minute intervals between −45 and 120 minutes through an indwelling venous cannula. Blood pressure was determined every 15 minutes throughout the test. The blood samples were centrifuged and the serum stored at −20°C until assay. Luteinising hormone and follicle stimulating hormone assays were performed by immunoradiometric assay kits from the North East Thames Regional Immunoassay Scheme in duplicates and the concentrations were measured as IU/l.

Table *Effects of clonidine on serum luteinising hormone and follicle stimulating hormone. Values are mean (SD)*

	Luteinising hormone (IU/l)	*Follicle stimulating hormone (IU/l)*
Study group (n=8)		
Basal	4·2 (1·1)	4·4 (1·7)
Peak after clonidine	5·1 (1·5)	4·3 (1·7)
Control (n=1)		
Basal	2·6 (0·7)	2·5 (0·6)
Peak after clonidine	2·4 (0·5)	2·6 (0·5)

No significant decrease in blood pressure was observed. The results shown in the table clearly show that clonidine does not have any effect on gonadotrophin concentrations.

$Alpha_1$ adrenergic blockers reduce the frequency of luteinising hormone pulses and suppress pulsatile release of luteinising hormone in animals, implying that the major effect of the alpha adrenergic system is to stimulate gonadotrophin releasing hormone release.[4] When clonidine was administered to rats with abolished luteinising hormone pulsatility, it re-established luteinising hormone pulsatility and increased the secretion of luteinising hormone.[2 3] The affinity of clonidine for the $alpha_1$ receptor is 70–500 times weaker than its affinity for $alpha_2$ receptor but it shows an effect on $alpha_1$ receptors when given in large doses.[5]

The reason why clonidine affected luteinising hormone pulsatility in the rats was that it was given in large doses. The small doses used in this study were effective on the $alpha_2$ receptors with no apparent effect on luteinising hormone pulsatility.

References

[1] Pintor C, Loche S, Corda R, *et al.* Clonidine treatment for short stature. *Lancet* 1987;**i**:1226–30.

[2] Estes KS, Simpkins JW, Kolra SP. Resumption with clonidine of pulsatile LH release following acute norepinephrin depletion in ovariectomized rats. *Neuroendocrinology* 1982;**35**:56–62.

[3] Kinoshita F, Nakai Y, Katakami H, Kato Y, Imura H. Role of alpha-adrenergic mechanism in regulating tonic luteinizing hormone release in conscious ovariectomized rats. *Endocrinology* 1981;**104**:1272–5.

[4] Kaufman J-M, Kesner JS, Wilson RC, Knobil E. Electrophysiological manifestation of luteinizing-hormone-releasing hormone pulse generator activity in the rhesus monkey: influence of alpha-adrenergic and dopaminergic blocking agents. *Endocrinology* 1985;**116**:1327–33.

[5] Krulich L, Mayfield MA, Steele MK, McMillen BA, McCann SM, Koenig JI. Differential effects of pharmacological manipulations of central alpha-1 and alpha-2 adrenergic receptors on the secretion of thyrotropin and growth hormone in male rats. *Endocrinology* 1982;**110**:796–804.

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Antenatal diagnosis and treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Sir,

Techniques of molecular biology have advanced to the point where we estimate that chorion villus biopsy can be informative for antenatal diagnosis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in over 95% of cases. This offers the possibility of treating mothers, who have previously delivered an index patient, with dexamethasone to prevent ambiguity of the genitalia of a potentially affected female fetus.

We are now in a position to offer this service to clinicians who are invited to contact us if we can be of assistance to them.

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Educating medical students about death and dying

Sir,

I read with interest the paper by Black *et al* on educating medical students about death and dying.[1]

Most students recognise the need for a course which equips them to deal with the needs of dying patients and their families and the subject is clearly worthy of a place in the already packed undergraduate curriculum. It seems unfair, even unkind, for a junior doctor to have to go through the ordeal of a consultation with the family of a terminally ill patient if he has not had the advantage of prior experience.

In my preclinical psychology course the subject was touched upon and, even at that stage, provoked lively discussion and debate. However, it was the 'communications course' which aroused the true feelings and emotions. This course is a challenging (and exhausting!) week of seminars, mini-lectures, group discussions, video teaching sessions, and role playing. Although aimed at learning general 'communication' skills—such as interviewing—the course inevitably included the setting of the terminally ill patient. Actors were brought in to help students learn about the breaking of bad news. Valuable feedback sessions enabled students to correct mistakes, such as distancing tactics, and to recognise scope for improvement.

Surely such a course is an essential component of the clinical curriculum. With the use of a range of teaching methods, medical students will have the chance to develop techniques in talking to dying patients and their families. Above all, the initial hurdle will have been jumped and the scene set for added understanding, trust and empathy in the doctor-patient relationship.

Reference

[1] Black D, Hardoff D, Nelki J. Educating medical students about death and dying. *Arch Dis Child* 1989;**64**:750–3.

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Annotation

Consent for children and adolescents who have an intellectual handicap

Every day paediatric practice probably raises a few queries concerning consent. Parents give their consent by proxy, based on what they believe is best for their child, determined largely by medical information and family custom. But there are several well known conundrums: there is the child with no living parents, the abandoned, handicapped child in the long stay hospital, the child in foster care, and the child who is at risk from his own family. There is also the child who cannot have blood transfusions for religious reasons. An unaccompanied minor is the term for a child refugee who may well have parents but in the havoc of war has become detached and is alone in a foreign country. Most of these situations are resolved by relying on precedent, and in the minority, by the use of legal procedures such as wardship or reception into care.

Current dilemmas concerning consent

Several incidents in the last 10 years have caused concern. There is the debate on how much information is necessary for consent to be fully informed, the question of minors who wish to give consent for contraception but expect confidentiality, and the dilemma of those who have reached their majority but remain unable to consent because of intellectual handicap.[1] Then there is the question of who can consent when the operation has eugenic overtones, such as sterilisation or abortion of both minors and adults who are unable to consent.

The child with intellectual handicap

Consent by proxy from caring parents will be the norm for intellectually handicapped children under 16 years, but if necessary the child can be made a ward of court or be received into care. While the procedures are no different for the handicapped child and his or her parents, there may be particular difficulties because of the presence of handicap. Parents, for example, may have difficulty in deciding to consent to a life saving operation on a multiply handicapped child, either at birth or later on. The outcome of standard surgical or medical intervention may be unclear because of the handicaps or parents may be asked for permission to involve their handicapped child in research procedures. Perhaps the most iniquitous of all is that they may be asked to sign a compulsory prospective 'cover all' consent form if their child is admitted to residential care, either for respite or permanently. These forms, of doubtful validity, cover anything from emergency medical treatment to horse riding and effectively pass day to day decision making to the professional care givers, who thus become both judge and jury.

The well versed non-accidental injury procedures do not always apply to handicapped children, partly because the norms of adequate care are often unclear and also because there may be no alternatives to parental care. The author well remembers a 14 year old child who had been trussed for days on the floor of the family home as the only means to stop him biting others. Despite every effort no procedure for non-accidental injury followed as it was known that hospital care was unacceptable to the family and no other facility was available.

Consent and legal competence

The law states that at 16 years the adolescent may be considered autonomous and legally competent to make decisions for himself, but the 16th birthday should be considered only as a mean age for the development of those decision making powers. Some will be competent earlier and some later and simple decisions will be made earlier than complex ones. Perhaps the 16 plus child is allowed his choice when this accords with parental wishes but not when it doesn't! However, others over 16 with intellectual handicap may never develop the understanding necessary for consent and it is on this last group that the spotlight has now been focused. Parental consent becomes invalid in law at the age of 16 years but no one else can give legally valid consent. This vacuum in the law is relevant to those with developmental intellectual handicap, those with severe head injuries, and those damaged by long standing mental illness or dementia.[2]

The search for a solution

The Mental Health Act (1959) dealt with involuntary detention in hospital and provided safeguards for mentally ill and mentally handicapped people so detained, as well as facilitating the development of community care. The sections on treatment without consent related to mental illness only.

This act of 1959 repealed a long series of acts to do with mental illness and intellectual handicaps, and in so doing the act revoked the Royal Prerogative whereby the Sovereign could act as 'parens patriae' and could issue a warrant to allow someone who was legally incompetent to receive necessary treatment or management. The last Royal Warrant was so issued in 1960.

It was hoped that the guardianship order in the 1959 act, a new concept in care, might take the place of that Warrant. The guardian (who could be a parent) was expected to treat the handicapped person as a young teenager and could sign consent forms on his behalf in addition to undertaking other parental duties. Very few guardianship orders were effected as prospective guardians were usually personnel of social services and the workload was seen to be substantial. In addition the law was little understood by parents who saw no reason to apply to be guardians as they continued to sign consent forms, which were acceptable to those who required them, neither party knowing that the system was of no legal standing. This mistake was often compounded by the use of a paediatric type of consent form, thus adding infantilism to invalid paternalism.

The Mental Health Act (1983) which replaced the 1959 act, produced restrictions on the role of guardians who could no longer sign consent forms, and the group of people with intellectual handicap, eligible for guardianship, was now limited to those who had abnormally aggressive or seriously irresponsible behaviour, the so called mentally impaired.

The National Assistance Act (1948) Section 47 can only be used to remove adults from their home against their will when there is total squalor in their living conditions and usually remediable illness. This act therefore has nothing to offer in the debate on consent.

The Court of Protection rules have been examined but this was set up to provide financial management for those who could not be personally responsible for their own affairs.

Neither does it seem sensible to rely on the 'double negative' declaration that a judge can give, that it would 'not be unlawful' to proceed with medical intervention. This is a way around the accusation of 'battery' that might follow if there is no consent and someone chose to contest the rightness of the intervention.[3]

While advocacy seems to be a possible solution, there are very few trained advocates available so far and the British model is that of a social best friend, rather than an advocate in law.[4]

The present situation for those over 16 who cannot give consent

With better lifestyles for those with intellectual handicap, involving choice making, taking risks, and standing by the consequences of personal decisions, many who are mildly, moderately, and even severely handicapped can make a simple choice if the situation is explained to them in terms they understand by someone they know and trust. Their vulnerability, however, must never be exploited by the unscrupulous who, by undue persuasion, may bias the choice that is made. Research is now being focused on the characteristics of the dialogue that allows maximum transfer of information and understanding.

There are times, however, when consent given by the handicapped person needs to be overruled. Such a person may feel very strongly about a certain matter and express their views but may not be able to see the full implications of what they are saying. They may have difficulty in long term planning and can only see the immediate future. The need to move from home when parents can no longer care may be essential, for example, but may be in direct opposition to the views of the handicapped person. They may refuse to consent to an operation on the basis that it might hurt. When such intervention is imperative and not controversial this lack of consent may be overridden using the doctrine of necessity.

At other times, naivety of the handicapped person may be misused in procedures that are nothing more than deceitful. Seclusion in a locked room is by definition done without consent and is a procedure that is safeguarded by rules and regulations in every district health authority. Some residences have a system whereby two door handles must be used simultaneously to open the door of such a room. If the client cannot operate the two door handles, then he is effectively secluded but may not be protected by the rules, an exploitation of his simplicity.

The position that we are in at present is clearly unsatisfactory. A substantial minority of people with intellectual handicap will never be able to give consent for themselves by virtue of the severity of their handicap or because of superimposed mental illness. The legal vacuum seems absolute and yet it is so little understood that time wasting procedures, such as asking parents to sign consent forms for adults, still continue. In the absence of consent of the person with intellectual handicap, the doctor acts 'in good faith' and shows 'a duty of care'. This applies to all care givers throughout the service and not only to the medical profession. It is, of course, good practice to obtain the agreement (but not the consent) of the next of kin, but there is no reason to hold up an emergency intervention until a relative can be found.

Where several lines of action are reasonable and possible and there is disagreement between the care giver and the family, then the care giver would be wise to seek further professional opinion with the family and to proceed cautiously. Often these issues are more social than medical—for example, about moving from long stay hospital to a house in the community, about expression of sexuality, and about risk taking in sporting holidays or road crossing programmes.

Most medical interventions are non-controversial but for high risk or doubtful outcome procedures the surgeon or physician would be wise to proceed only when he has the backing of a second or even a third professional opinion. Should the procedure involve research, with little or no benefit to the patient, be controversial, or have social as well as medical repercussions,[5–7] such as sterilisation with or without abortion, full consultation with the legal profession and with the ethics committees are essential. Without this the medical profession must expect to be confronted by non-medical personnel and those representing the human rights movements, whatever the age of the patient.

The age of enlightenment

The vast majority of consent dilemmas can be overcome by resorting to wider medical consultation, involving the family, ethics committees, and occasionally the law, but a lot is left to the discretion of the caring personnel. There is, however, reason to hope for legal clarification soon.[8] In a recent case where sterilisation was requested for a women with profound intellectual handicap and where the medical opinions for sterilisation were almost unanimous, responsibility for the ultimate decision was passed from the High Court to The Court of Appeal and thence to The House of Lords. It is to be hoped that out of this expensive and time consuming exercise, rules will soon emerge that can be used in future similar situations. It may be that a hierarchial system is developed whereby straightforward decisions of minor import are decided at the grass roots level and with involvement of the family. Decisions of greater complexity may be dealt with at the level of the district health authority and the most complex by a committee with medical, legal, ethical, and lay representation. A similar committee is already set up in New York.[9] Whatever the details, almost certainly the overriding philosophy will be to 'act in the best interests of the patient', however complex are the variables.

It must, of course, remain essential that the decision for one patient will not become the slippery slope for others. It is important that controversial decisions are not promoted on the basis of racial hygiene: it is a matter of ensuring that people who are legally incompetent have the best possible decisions made for them in the light of current knowledge.

Action that can be taken now

There is much to be done with what we know already. Each health authority should ensure that day to day procedures, in the accident and emergency department for example, acknowledge the rights of the patient, understand the concept of legal competence, the role of the care giver, and the decision making responsibility of the doctors. Explanation and education for medical students, doctors, and nurses are essential. A leaflet on every notice board in wards and departments, given to all new doctors and put in outpatient letters where the patient is known to be legally incompetent can outline the current situation and where to go for advice (TR Gould, J Bicknell, unpublished). Each health authority must be encouraged to adopt whatever procedure emerges from the current legal deliberations. Most ethics committees look at only research at present, but may in the future be required to look at clinical decisions in the absence of consent. Above all, the practicalities need to be so straightforward for outpatients and inpatients at ward and departmental level that legal incompetence does not become yet another reason for those with intellectual handicaps to be seen as awkward customers of the health service.

References

[1] Gillon R. Where respect for autonomy is not the answer. Philosophical medical ethics. *Br Med J* 1986;**292**:48–9.

[2] Memorandum by the Law Society's Mental Health Sub Committee, *Decision making and mental incapacity: a discussion document*. London: The Law Society, 1989.

[3] Dyer C. Judges cast doubt on law of consent. *Guardian* 1989 Jan 17:1.

[4] Institute of Medical Ethics. Consent and the incompetent. *Bulletin of the Institute of Medical Ethics* 1989;**47**:3.

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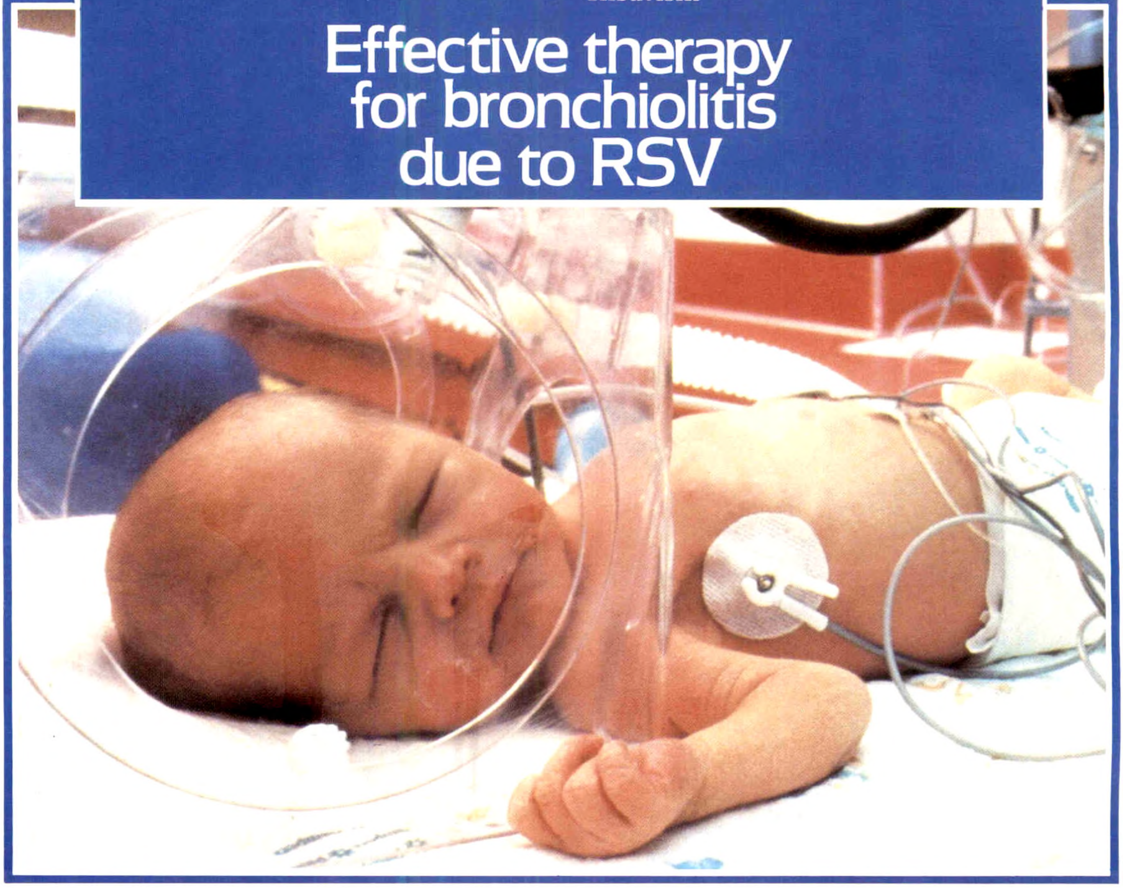

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Original articles

Serial ^{99m}Tc dimercaptosuccinic acid (DMSA) scans after urinary infections presenting before the age of 5 years

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SUMMARY Forty five children presenting with a first proven urinary tract infection under the age of 5 years were studied by sequential ^{99m}Tc dimercaptosuccinic acid (DMSA) scans. Forty nine kidneys in 40 children had definite defects at presentation, and 39 (80%) of these defects were still present when the DMSA scan was repeated. Changes in the appearance of defects were independent of the presence or degree of reflux at presentation and of symptomatic recurrence of infection, though the combination of new infection and grade 3 reflux (reflux reaching the renal calices with distension) was associated with deterioration. No kidney with a relative DMSA uptake of less than 35% showed any improvement in its cortical defects. Only two kidneys that were initially without defects, in a single patient who had bilateral grade 3 reflux and breakthrough infections, developed defects on subsequent scans.

The outcome after urinary tract infection is dependent on the effect of the first infection on the kidney. Occasionally children with grade 3 reflux develop damage during subsequent infections. More widespread use of DMSA scans should improve our understanding of the factors that determine the development of renal damage.

Urinary tract infections in young children, particularly when they are associated with vesicoureteric reflux, can lead to renal scarring[1 2] and subsequently to renal dysfunction and hypertension.[3] The difficulty of recognising vesicoureteric reflux before the first urinary tract infection has focused attention on the prevention of new scarring after the first infection.[4] It is uncertain how much scarring is sustained at the time of first infection, and how much is the result of repeated infections and thus (in theory) preventable. Serial studies of kidneys have used excretory urography[5 6] but as this technique can take up to two years to show the full extent of scarring[6 7] it makes the positive identification of new scars difficult. ^{99m}Tc dimercaptosuccinic acid (DMSA) scans are more sensitive for detecting early renal defects, especially in the under 5 age group,[8 9] and the relative uptake of DMSA can be measured to give an objective measurement of renal function in unilateral damage. The appearance of new defects on subsequent scans is likely to be due to new lesions rather than the contraction of original scars by fibrosis, as shown by excretory urography.

We have now carried out second DMSA scans on 45 children who were originally scanned shortly after a first urinary tract infection, and we report the changes.

Patients and methods

Over a three year period (1982–4) 115 children under the age of 5 years presented with a symptomatic, microbiologically proved, urinary tract infection. None of the children had a history of previous urinary tract infections or of recurrent fevers of unknown origin. A DMSA scan was performed as part of an investigation protocol that also included intravenous urography and ultrasonography, and micturating cystourethrography in selected patients. The methods and the results have been reported previously.[9]

Thirty nine of the 115 children, and a further six children seen since 1984 who also presented with a first symptomatic urinary tract infection, have now had further DMSA scans and this was the criterion for inclusion in this study. The decision to repeat the scan was taken on clinical grounds by the child's clinician, and reasons included an abnormal first DMSA scan, and detection of vesicoureteric reflux or further urinary tract infection, or both. There were 15 boys and 30 girls. All of them had had a micturating cystourethrogram and a DMSA scan within a month of presentation. In addition all had either an ultrasound scan or an intravenous urogram, and 18 had both.

The mean age at the time of the first scan was 2·04 years (range 12 days to 4·9 years) and at the time of the second scan 4·29 years (range 33 weeks to 9·5 years). The mean interval between scans was 2·25 years (range 25 weeks to 6·3 years).

Reflux seen on the micturating cystourethrogram was recorded on a scale of 1 to 3 (grade 1—confined to the ureter; grade 2—reaching the renal calices, without distension; and grade 3—reaching the renal calices, with distension). All children with reflux received continuous prophylactic antibiotics in the period between the two DMSA scans or, in 17 cases where reflux was corrected surgically, until six months after operation.

The results of the DMSA scans were reviewed without knowledge of other imaging results or of the clinical course. Each kidney was classified as being abnormal (showing a definite cortical defect or having diffuse abnormality of DMSA uptake), as having a possible cortical defect, or as being normal. The finding of diffuse abnormality was recorded independently of the relative percentage uptake. The kidneys on the second scan were similarly classified and in addition assessed as deteriorated, unchanged, or improved, compared with the first scan. Relative DMSA uptake was measured in 89 of the 90 scans performed.

Results

In the 45 children the initial cystogram showed 15 had no reflux, 11 had unilateral reflux, and 19 bilateral reflux. Of the 49 refluxing kidney units eight had grade 1, 18 had grade 2, and 23 had grade 3 reflux. Seventeen children had operations to correct reflux in 27 kidneys, including 12 with grade 3 reflux. Cystography was not repeated as part of the study except when clinically indicated (when operation was being considered or before stopping antibiotic prophylaxis).

KIDNEYS THAT INITIALLY SHOWED DEFINITE ABNORMALITIES

Forty nine kidneys in 40 children initially showed abnormalities. Forty of them (80%) still showed defects at follow up. Eight defects were improved but still definite, 28 were unchanged, and four had deteriorated. The remaining nine kidneys had no defects at follow up. The time between scans in this group was significantly shorter than in those kidneys where the defects persisted (median time 0·7 years compared with 2·5 years, $p<0·01$ Mann-Whitney U test). None of the children whose renal defects resolved had breakthrough infections compared with 11 in children with persisting defects. This difference was not significant. There was no association between changes in the appearance of the kidneys on the DMSA scans and the presence or degree of reflux at presentation.

KIDNEYS THAT INITIALLY SHOWED POSSIBLE DEFECTS

Nine kidneys initially showed possible defects. The uptake of DMSA in those with contralateral normal kidneys was in the normal range of 43–57% (median 50·5%) and was significantly higher than kidneys with definite defects (median 40% $p<0·01$ Mann-Whitney U test). Three of the defects had disappeared on subsequent scanning, and the six that persisted remained equivocal, none showing deterioration into definite defects. For the purpose of this analysis we have reclassified these kidneys as normal and included them with the 32 kidneys with no defects.

Table 1 *Change in appearance of scan in 90 kidneys*

Outcome	*Breakthrough infection (n=26)*		*No breakthrough infection (n=64)*		*Total*
	Reflux (grade 3)	*No reflux (reflux surgically corrected)*	*Reflux (grade 3)*	*No reflux (reflux surgically corrected)*	
No defect on either scan	4 (1)	7 (2)	3 (1)	25 (7)	39
Resolved or improving defect	2 (2)	0	2 (0)	13 (4)	17
Unchanged defect	2 (2)	7 (6)	5 (1)	14 (8)	28
Deteriorating defect	1 (1)	1 (0)	1 (1)	1 (0)	4
New defect	2 (2)	0	0	0	2
Total	11 (8)	15 (8)	11 (3)	53 (19)	90

KIDNEYS THAT INITIALLY LOOKED NORMAL

Forty one kidneys initially looked normal; five children had two normal kidneys and 31 had one normal kidney. Thirty two kidneys had no reflux, or reflux that was subsequently surgically corrected, and seven of these had been exposed to breakthrough infection. Three kidneys had uncorrected reflux (two had grade 2, and one had grade 3) but there were no breakthrough infections. None of these 35 kidneys developed defects. Six kidneys had breakthrough infections in the presence of reflux (three had grade 1, and three had grade 3). Two of these latter kidneys (in the same child) developed widespread defects.

The outcome in the 90 kidneys is shown in table 1. There was no correlation between changes in appearance between the two scans and the presence of reflux alone, or in the occurrence of breakthrough infection alone, but kidneys with grade 3 reflux *and* breakthrough infection were at greater risk of deteriorating (three of eight kidneys) than those without this combination (three of 82) ($p=0.001$, Fisher's exact test, two tailed).

CHILDREN WITH UNILATERAL DEFECTS

When one kidney was normal by all imaging techniques (DMSA scan together with intravenous urography or ultrasound scan, or both) it was reasonable to assume that this kidney was also functionally normal and therefore any reduction in relative DMSA uptake by an affected contralateral kidney was considered to indicate an absolute loss of function. There were 30 children with abnormal DMSA scans of one kidney who met this criterion and in whom the divided DMSA uptake was measured. There was a close association between DMSA uptake in kidneys at the first and at the second scan (figure) indicating that the lesion sustained at the first infection was the main determinant of functional outcome.

There was no difference in mean relative uptake of DMSA at the first scan in kidneys with all grades of reflux ($n=16$, median 39%), or with grade 3 reflux ($n=9$, median 40%), compared with those without reflux ($n=14$, median$=42.5$%).

There was no difference between the mean relative uptake by kidneys at the first scan and the subsequent scan either in the group as a whole or when they were classified by the presence or degree of reflux, or the occurrence of breakthrough infection during the follow up period (table 2).

There was a significant difference between the initial mean uptake of DMSA by those kidneys in which cortical defects subsequently improved compared with those that showed no improvement ($p<0.05$, Mann-Whitney U test). No kidney with an uptake of less than 35% showed any improvement of associated cortical defects.

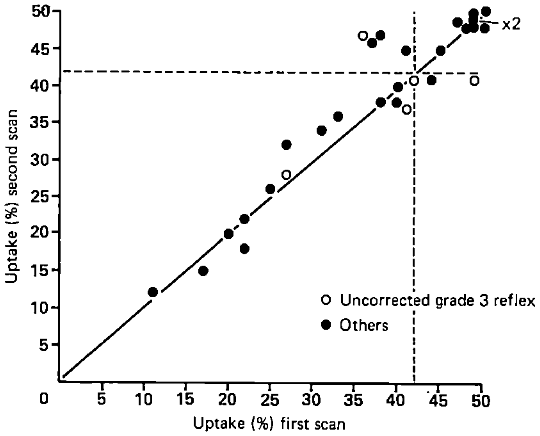

Figure *DMSA uptake at first and subsequent scans in kidneys with unilateral renal defects ($n=30$). Solid line, $x=y$ (r 0·938, $p<0.001$); dashed line, lower limit of normal (42% uptake).*

Table 2 *DMSA uptake at first and subsequent scans in 30 kidneys with unilateral defects*

	No of kidneys	*Mean percentage uptake*		*Difference between means*	*SEM*	*p Value*
		First scan	*Second scan*			
Breakthrough	7	36·3	36	0·29	2·14	>0·8
All reflux	8	41·6	40·1	−0·25	1·96	>0·9
Grade 3 reflux	5	39	38·8	0·2	3·18	>0·9
Grade 3 reflux plus breakthrough	3	42·3	43	0·66	1·46	>0·6
All kidneys	30	37·2	38	0·76	0·73	>0·3

Reflux includes only those that were not surgically corrected.

Discussion

When cortical defects are present on initial DMSA scans there is a high risk of permanent damage to the kidney. It has been suggested that some defects seen on scans carried out within three months of a urinary tract infection may be transient[10] and this has led to the idea that scans should not be carried out within this period.[11] In our series 80% of such changes persisted. We believe that waiting for three months before carrying out a scan is undesirable, as it will result in delay in identifying children with kidneys at risk.

The transient defects probably represent focal bacterial nephritis that resolves; recent experimental work has shown that kidneys with defects on DMSA scan after infection and reflux always have a corresponding pathological lesion, but this is not always permanent.[12]

We examined the hypothesis that defects may disappear when there is a long interval between the scans, but—on the contrary—the findings showed that these children had been rescanned at shorter intervals than those children whose defects persisted and that disappearance of defects would therefore seem to be independent of the interval between scans.

The follow up scans showed that equivocal cortical defects are unlikely to be associated with long term renal damage. This makes the scans easier to assess, as minor variations in cortical outline (which may represent fetal lobulation) can be interpreted as normal by the radiologist.

This series has confirmed that kidneys that were not damaged by a first infection may occasionally develop appreciable scarring after subsequent infections as has been previously described,[5 6] but in our series this was only seen in one child who had bilateral grade 3 reflux. The reason that we found so few new scars might be because DMSA scanning is more sensitive in detecting initial parenchymal changes than intravenous urography, upon which earlier studies depended.[5]

Most renal defects remained unchanged regardless of features on presentation or the subsequent clinical course. This suggests that for most kidneys the initial infection determines the subsequent degree of damage, and later breakthrough infection makes little difference if grade 3 reflux is not also present. This supports the work of Ransley and Risdon, who suggested that those kidneys susceptible to parenchymal infection because of their papillary morphology will become damaged at the first infection (the so called 'big-bang' theory).[13]

Where renal damage was unilateral, the initial relative DMSA uptake was a useful guide to later outcome, and no kidney with a relative uptake of less than 35% recovered. When relative uptake was in the accepted normal range (43–57%[14]), however, kidneys could show either temporary or permanent defects. There are limitations to the use of relative DMSA uptake because ipsilateral deterioration cannot be distinguished from contralateral compensatory hypertrophy[15] and the measurement is of little value in the presence of bilateral disease. The recently described technique for measurement of absolute uptake of DMSA in each kidney will allow more precise quantitation of the progress of an individual kidney and allow functional assessment of bilateral impairment.[14] An interesting feature of our original cohort was the high incidence of defects in the absence of reflux.[9] Twelve of these 26 kidneys had persistent defects on repeat scans, in six the defects improved, and eight have not been rescanned. Assuming that there were no false negative micturating cystourethrograms, this suggests that at least 18% of permanent renal defects develop in the absence of reflux compared with the 2% previously reported in a study in which intravenous urography was accepted as the standard.[16]

Further studies of the genesis of renal scarring by DMSA scans, including measurement of absolute DMSA uptake, will improve our understanding of the factors that determine the development of chronic pyelonephritis. The present uncertainty about the natural history of renal scarring is resulting in a worrying lack of consensus among paediatricians about the investigation and management of urinary tract infections.[17] More widespread availability and use of DMSA renal scans should help to resolve some of the unanswered questions.

We thank the consultant paediatricians of Merton and Sutton, mid Surrey, and east Surrey health authorities for referring their patients for investigation, and Dr VR McCready and the staff of the department of nuclear medicine, Royal Marsden Hospital, for carrying out the scans.

References

[1] Smellie JM, Hodson CJ, Edwards D, Normand ICS. Clinical and radiological features of urinary infection in childhood. *Br Med J* 1964;ii:1222–6.

[2] Scott JES, Stansfeld JM. Ureteric reflux and kidney scarring in children. *Arch Dis Child* 1968;**43**:468–70.

[3] Kincaid-Smith P, Becker GJ. Reflex nephropathy in the adult. In: Hodson CJ, Kincaid-Smith P, eds. *Reflex nephropathy*. New York: Masson, 1979:21–8.

[4] Birmingham Reflux Study Group. Prospective trial of operative v non-operative management of severe vesicoureteric reflux: 2 years observation in 96 children. *Br Med J* 1983;**287**:171–4.

[5] Smellie JM, Ransley PG, Normand ICS, Prescod N, Edwards D. Development of new renal scars—a collaborative study. *Br Med J* 1985;**290**:1957–60.

[6] Filly R, Friedland GW, Govan DE, Fair WR. Development and

progression of clubbing and scarring in children with recurrent urinary tract infections. *Radiology* 1974;**113**:145–53.

[7] Hodson CJ, Wilson S. Natural history of pyelonephritic scarring. *Br Med J* 1965;**ii**:191–9.

[8] Monsour M, Azmy AF, MacKenzie JR. Renal scarring secondary to vesicoureteric reflux. Critical assessment and new grading. *Br J Urol* 1987;**60**:320–4.

[9] Verber IG, Strudley MR, Meller ST. ^{99m}Tc dimercaptosuccinic acid (DMSA) scan as first investigation of urinary tract infection. *Arch Dis Child* 1988;**63**:1320–5.

[10] Merrick MV, Uttley WS, Wild SR. The detection of pyelonephritic scarring in children by radio-isotope imaging. *Br J Radiol* 1980;**53**:544–56.

[11] Thelle T, Biskjaer N. Combined (99m TC) DMSA kidney scintigraphy and (131/I) Hippuran renography in children with urinary tract infections. *Acta Paediatr Scand* 1985;**74**:720–5.

[12] Parkhouse HF, Godley ML, Cooper J, Risdon RA, Ransley PG. Renal imaging with ^{99}Tc^{m}DMSA in the detection of acute pyelonephritis; an experimental study in the pig. *Nucl Med Commun* 1989;**10**:63–70.

[13] Ransley PG, Risdon RA. Papillary morphology in infants and young children. *Urol Res* 1975;**3**:111–3.

[14] Gordon I, Evans K, Peters AM, *et al.* The quantitation of ^{99}Tc^{m}DMSA in paediatrics. *Nucl Med Commun* 1987;**8**:671–80.

[15] Claesson I, Jacobsson B, Jodal U, Winberg J. Compensatory kidney growth in children with urinary tract infection and unilateral renal scarring; an epidemiological study. *Kidney Int* 1981;**20**:759–64.

[16] Shah KJ, Robins DG, White RHR. Renal scarring and vesicoureteric reflux. *Arch Dis Child* 1978;**53**:210–7.

[17] Smyth RL, Berman L, Valman HB. Current practice in managing urinary tract infections in children. *Br Med J* 1988;**297**:1516–7.

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Vesicoureteric reflux: screening of first degree relatives

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SUMMARY Thirty three healthy infants and children with a family history of reflux nephropathy or vesicoureteric reflux in first degree relatives were screened for upper urinary tract abnormalities (renal scarring or pelvicaliceal dilatation) using ultrasound scanning or intravenous urography, or both. In addition, micturating cystourethrography was carried out in all infants and children under 2 years old (n=20) and in children over 2 years old in whom abnormalities of the upper renal tract (renal scarring) had been found (n=3). Upper renal tract abnormalities were found in four of the total of 33 children (12%) and vesicoureteric reflux in 12 of the 23 who underwent micturating cystourethrography (52%). Screening of infants and children was acceptable to parents. This approach has enabled the diagnosis of vesicoureteric reflux to be made in an appreciable number of children before the development of urinary tract infections and reflux nephropathy. Prospective follow up of this group will provide more information about the natural history of sterile vesicoureteric reflux.

The association of vesicoureteric reflux, urinary tract infection, and reflux nephropathy is well established.[1] Reflux nephropathy is thought to account for at least 10% of cases of end stage renal disease.[2] This may be an underestimate, as reflux nephropathy is commonly underdiagnosed. The incidence of hypertension in children with reflux nephropathy is between 5% and 30%.[3 4] In infants with vesicoureteric reflux renal damage commonly follows urinary tract infection. When vesicoureteric reflux is diagnosed in an infant after the first urinary tract infection scarring in susceptible areas of the kidney may already be developing so that attempts to prevent renal damage by giving prophylactic antibiotics or by reimplanting the ureters are made after the initial damage has occurred. Late presentation of patients with end stage renal disease as a result of reflux nephropathy is common, and some have little or no history of preceding urinary tract infection.[5] In these children, the urinary tract infection may have been present but undiagnosed or, alternatively, damage may have been caused by sterile vesicoureteric reflux.[6] As vesicoureteric reflux is normally detected after the presenting infection there has been little opportunity to observe the natural history of sterile vesicoureteric reflux in children.

There have been a number of reports indicating the familial nature of vesicoureteric reflux.[7] Investigation of the HLA system has shown that haplotypes A2–B8 and A9–B12 occur more commonly in children with reflux nephropathy.[8 9] Because of the evidence in favour of a familial tendency for vesicoureteric reflux and reflux nephropathy, it is appropriate to give genetic counselling to affected families so that they are aware of potential problems such as the risk of urinary tract infection, vesicoureteric reflux, and reflux nephropathy, as well as the complications of reflux nephropathy. Nevertheless screening for vesicoureteric reflux is not recommended routinely.

Smellie *et al* reported that long term prophylaxis in children with symptomatic urinary tract infections prevented reinfection and aided renal growth.[10] Children with vesicoureteric reflux during infancy and early childhood are more prone to develop reflux nephropathy following urinary tract infections and hence long term prophylaxis is indicated in the most vulnerable group of children—those under 2 years of age. This report describes our clinical experience in counselling families with reflux nephropathy or vesicoureteric reflux.

Patients and methods

Twenty seven families in which one member had vesicoureteric reflux, or reflux nephropathy, or both, were counselled about the familial risk of vesicoureteric reflux and the subsequent risk of reflux nephropathy, as well as the risk and symptoms of urinary tract infection, particularly in infancy. Two groups of children were studied. Group A comprised 17 children born to 15 affected mothers, 14 of whom had been identified in childhood during a programme of screening for bacteriuria.[11] The remaining mother had had a urinary tract infection in childhood and had subsequently presented with hypertension in pregnancy caused by reflux nephropathy. Group B comprised 16 siblings of 11 children who presented with clinically apparent urinary tract infection.

Ultrasound examination of the kidneys and bladder was undertaken in every case to assess renal size, the presence of pelvicaliceal dilatation and

Table 1 *Infants and children of parents (index cases) with reflux nephropathy or vesicoureteric reflux*

Diagnosis of index case	*Case No*	*Age*	*Sex*	*Findings on intravenous urography or ultrasound scanning*	*Findings on micturating cystourethrography*
Reflux nephropathy	1	3 Weeks	Male	Normal	Normal
Vesicoureteric reflux	2	1 Month	Female	Normal	Refused
Reflux nephropathy	3	6 Weeks	Female	Normal	Bilateral vesicoureteric reflux grade II
Reflux nephropathy	4	2 Months	Female	Dilated calyces	Normal
Reflux nephropathy	5	2 Months	Female	Normal	Normal
Reflux nephropathy	6	2 Months	Female	Normal	Normal
Reflux nephropathy	7	3 Months	Female	Normal	Normal
Reflux nephropathy	8	3 Months	Male	Normal	Refused
Reflux nephropathy	9	4 Months	Male	Normal	Normal
Reflux nephropathy	10	6 Months	Female	Normal	Bilateral vesicoureteric reflux grade II
Reflux nephropathy	11	7 Months	Female	Normal	Bilateral vesicoureteric reflux grade II
Reflux nephropathy	12	10 Months	Male	Normal	Bilateral vesicoureteric reflux grade I
Vesicoureteric reflux	13	10 Months	Male	Normal	Normal
Reflux nephropathy	14	16 Months	Male	Normal	Bilateral vesicoureteric reflux grade I
Reflux nephropathy	15	3 Years	Female	Normal	Not done
Reflux nephropathy	16	4 Years	Male	Normal	Not done
Reflux nephropathy	17	4 Years	Male	Normal	Not done

Table 2 *Siblings of children (index cases) with reflux nephropathy or vesicoureteric reflux*

Diagnosis of index case	*Case No*	*Age*	*Sex*	*Findings on intravenous urography or ultrasound scanning*	*Findings on micturating cystourethrography*
Reflux nephropathy	1	3 Weeks	Female	Normal	Normal
Vesicoureteric reflux	2	5 Weeks	Female	Normal	Left vesicoureteric reflux grade I
Hypoplastic right kidney and vesicoureteric reflux	3	7 Weeks	Female	Normal	Bilateral vesicoureteric reflux grade I
Single kidney, reflux nephropathy	4	2 Months	Male	Normal	Left vesicoureteric reflux grade II
Single kidney, reflux nephropathy	5	2 Months	Male	Normal	Normal
Bilateral vesicoureteric reflux	6	2 Months	Male	Normal	Bilateral vesicoureteric reflux grade II
Bilateral vesicoureteric reflux	7	9 Months	Female	Normal	Left vesicoureteric reflux grade II
Reflux nephropathy	8	9 Months	Female	Normal	Left vesicoureteric reflux grade I
Reflux nephropathy	9	2 Years	Female	Scarred left kidney	Normal
Reflux nephropathy	10	3 Years	Male	Normal	Not done
Reflux nephropathy	11	3 Years	Female	Normal	Not done
Reflux nephropathy	12	4 Years	Female	Scarred right kidney	Right vesicoureteric reflux grade II
Reflux nephropathy	13	6 Years	Male	Normal	Not done
Reflux nephropathy	14	9 Years	Male	Normal	Not done
Reflux nephropathy	15	9 Years	Male	Normal	Not done
Reflux nephropathy	16	10 Years	Female	Bilateral scarred kidneys	Normal

gross renal scarring. Four children also underwent intravenous urography before 1984 when experience in ultrasound examination was limited. Infants and children under 2 years of age were advised to undergo micturating cystourethrography, which was also recommended in older children if upper tract abnormality such as pelvicaliceal dilatation or renal scarring had been detected on intravenous urography or ultrasound examination. The grading of vesicoureteric reflux was classified according to the recommendations of the Medical Research Council Bacteriuria Committee.[12] To reduce the risk of urinary tract infection trimethoprim 2 mg/kg was given in three doses at 12 hour intervals, one dose before and two after catheterisation, to all children undergoing micturating cystourethrography. Children under the age of 2 years in whom vesicoureteric reflux was detected were advised to take low dose prophylaxis with trimethoprim, 1 to 2 mg/kg/day until the age of 2 years. These cases are reviewed individually after the age of 2 years and a decision then made about stopping or continuing the prophylaxis, depending on whether breakthrough infections occurred during the period of follow up.

Results

In Group A the acceptability of micturating cystourethrography was 86%, whereas in group B it was 100%. Four of the total of 33 children (12%) had an abnormality of the upper renal tract (one child had a dilated caliceal system and three had scarring of kidneys). Twelve out of the 23 children who underwent micturating cystourethrography (52%) had vesicoureteric reflux. Ten of these children were under 1 year of age. The reflux was grade I in five cases and grade II in seven cases. Fifteen of 33 children (45%) showed some abnormality of the renal tract on ultrasound examination or micturating cystourethrography, or both (tables 1 and 2). All six abnormalities found in group A and six of the nine in group B were in children under 2 years of age.

Discussion

To justify screening it is necessary to detect an early form of a condition so that serious problems can be prevented. Our knowledge of the natural history of reflux nephropathy suggests that this may be the case in this condition. Although it may be possible to prevent renal damage in healthy infants with vesicoureteric reflux by preventing urinary tract infection with long term low dose prophylaxis, this has not been proved. Despite the fact that grade I vesicoureteric reflux has a high spontaneous resolution rate and may not be well correlated with reflux nephropathy, we have recommended chemoprophylaxis as all these children were in the most vulnerable age group, that is, under 2 years of age.

Twenty four families, all of whom had previous experience of micturating cystourethrography, allowed their children to undergo this examination. The acceptability was 100% if other siblings had already had clinical problems (group B). In group A, in which index cases were asymptomatic women who were diagnosed in a bacteriuria survey during childhood and who had few problems except during pregnancy, the acceptability was slightly lower (86%). The cost effectiveness of this type of programme cannot be assessed from this study as it is not possible to detect how many scars have been prevented. Because over half of those infants investigated by micturating cystourethrography had vesicoureteric reflux, however, the potential for the prevention of scarring is considerable. In addition, older children with established reflux nephropathy were also identified. In these children a diagnosis of urinary tract infection had never been previously considered. In this group it was possible to give advice about the risk of progression of scarring, hypertension, and possible complications during pregnancy.

The diagnosis of urinary tract infection in infants is not easy, as symptoms are rarely localised to the urinary tract. Unless an infant is referred to hospital for investigations, urine is rarely examined for a urinary tract infection within the community. During the process of counselling and screening, families are instructed to consider the possibility of urinary tract infection if their infant becomes ill, and arrangements are made through the general practitioner or by direct access to the ward to check the urine when necessary. Selective screening for vesicoureteric reflux has enabled us to identify a population who are at high risk of developing reflux nephropathy, and to follow them up prospectively. With this technique it is possible to improve the degree of health care provided for those children who are at greatest risk of developing reflux nephropathy. Long term follow up of these infants will enable more to be learnt about the natural history of sterile vesicoureteric reflux.

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References

[1] Bailey RR. An overview of reflux nephropathy. In: Hodson C J, Kincaid-Smith P, eds. *Reflux nephropathy*. New York: Masson, 1979:3–13.

[2] Donckerwolcke RA, Brunner FP. *Combined report on regular*

dialysis and transplantation of children in Europe 1981. Proceedings of the European Dialysis and Transplant Association. Volume 20. London: Pitman Medical, 1982:60–91.

[3] Bachman H. Hypertension: a frequent complication in children and adolescents with reflux nephropathy. *Klin Padiatr* 1982;**194:** 152–8.

[4] Bailey RR. Reflux nephropathy and hypertension. In: Hodson CJ, Kincaid-Smith P, eds. *Reflux nephropathy,* New York: Masson, 1979:263–7.

[5] Heale WF, Shannon FT, Utley WLF, Rolleston GL. Familial and hereditary reflux nephropathy. In: Hodson CJ, Kincaid-Smith P, eds. *Reflux nephropathy*. New York: Masson, 1979: 48–52.

[6] Ransley PG, Risdon RA, Godley ML. High pressure sterile vesicoureteric reflux and renal scarring: an experimental study in the pig and minipig. In: Hodson CJ, Hepinstall RM, Winberg J, eds. *Reflux nephropathy update 1983*. London: Karger, 1984:320–43.

[7] Bailey RR, Janus E, McLoughlin K, Lynn KL, Abbott GD. Familial and genetic data in reflux nephropathy. In: Hodson CJ, Hepinstall RM, Winberg J, eds. *Reflux nephropathy update 1983*. London: Karger, 1984:40–51.

[8] Bailey RR, Wallace M. HLA–B12 as a genetic marker for vesicoureteric reflux? *Br Med J* 1978;**i:**48–9.

[9] Torres VE, Moose SB, Kurtz SB, Offord KP, Kelalis PP. In search of a marker for genetic susceptibility to reflux nephropathy. *Clin Nephrol* 1980;**14:**217–20.

[10] Smellie JM, Edwards D, Normand ICS, Prescod N. Effect of vesicoureteric reflux on renal growth in children with urinary tract infection. *Arch Dis Child* 1981;**56:**593–8.

[11] McLachlan MSF, Meller ST, Verrier Jones ER, *et al.* Urinary tract in schoolgirls with covert bacteriuria. *Arch Dis Child* 1975;**50:**253–8.

[12] A Report by the members of the Medical Research Council Bacteriuria Committee. Recommended terminology of urinary tract infection. *Br Med J* 1979;**ii:**717–9.

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Congenital diaphragmatic defects that present late

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SUMMARY Twenty two patients (age range: 1 month to 11 years) were treated for congenital diaphragmatic defects (excluding hiatus hernia) in the six year period 1983–8. Presenting features were failure to thrive (n=7), abdominal pain and vomiting (n=4), chronic respiratory symptoms (n=3), and inability to wean from ventilatory support (n=3). The defect was an incidental finding in five patients. Operative repair was performed with no mortality or serious postoperative morbidity. Dramatic improvement occurred in 15 of the 17 symptomatic patients. Awareness of the differential diagnosis should avoid delay in diagnosis or inappropriate treatment. Surgical correction is strongly recommended in all cases.

Excluding hiatus hernia there are two types of congenital diaphragmatic defect—hernia and eventration. A hernia is a protrusion of the abdominal viscera through the diaphragm with or without a hernial sac. An eventration may be defined as an abnormally high leaf of an intact diaphragm as a result of paralysis, aplasia, or atrophy of the muscle fibres. Its uninterrupted continuity differentiates it from a hernia.[1]

Between 5% and 30% of congenital defects present after the neonatal period,[1 2] but despite this high incidence congenital diaphragmatic defects are not often recognised. This results in diagnostic delay and inappropriate treatment, both of which may be fatal.[3–5] Most reports refer only to true diaphragmatic hernias and exclude eventration. As both present in a similar manner and cannot always be differentiated before operation, we believe that eventrations should be included. The purpose of this paper is to draw attention to these defects and the circumstances leading to diagnostic delay and inappropriate treatment.

Patients and methods

The records of patients over 1 month of age with congenital diaphragmatic defects treated in this unit from 1983 to 1988 were retrospectively reviewed. Patients with acquired lesions were excluded. There were 22 patients (13 girls and nine boys) who represent 13% of all the congenital diaphragmatic defects treated during this period. Age at operation ranged from 1 month to 11 years (median 9 months). There were 18 hernias and four eventrations (table 1). Associated abnormalities included midgut malrotation (n=8) and the Prader-Willi syndrome with Langerhans cell histiocytosis (n=1). No other associated congenital anomalies were noted, but four patients had group B β haemolytic streptococcal infection.

Presenting features are listed in table 2. Three of the seven patients who failed to thrive also had

Table 1 *Types of defects*

	Sac present	*Left*	*Right*	*Bilateral*
Bochdalek hernia (n=10)	5	8	2	0
Central hernia (n=5)	2	2	3	0
Morgagni hernia (n=3)	1	0	3	0
Eventration (n=4)	Not applicable	0	3	1

Table 2 *Presenting features*

	No of infants
Failure to thrive	7
Abdominal pain and vomiting	4
Chronic respiratory symptoms	3
Inability to breath without ventilator	3
No symptoms (incidential finding)	5
Total	22

dyspnoea during feeding. All three patients who were dependent on ventilatory support were premature and required ventilation soon after birth for primary lung disease. The defects were all right sided, and a pleural effusion was erroneously diagnosed and chest drain inserted in each case. One of these patients suffered a catastrophic haemorrhage as a result of trauma to the intrathoracic liver necessitating emergency thoracotomy. The five patients in whom the defect was an incidental finding presented with symptoms unrelated to the diaphragmatic defect. Three had upper respiratory tract infections, one had otitis media, and one had Langerhans cell histiocytosis. The clinical impression of dextrocardia was the indication for chest radiograph in three patients. A routine 'staging' radiograph was carried out in the patient with histiocytosis, but the indication for radiography in the remaining patient was not clear.

Diagnostic confusion occurred in three patients, two of whom had abnormal radiographs at the referring hospitals but normal ones on admission to this unit. Subsequent pictures showed the defect in one patient, while in the remaining patient a hernia was confirmed at operation. One patient with an eventration had an initial normal chest radiograph, followed by radiographs showing the raised hemidiaphragm. As the initial picture was normal the correct diagnosis was not immediately considered. In these patients diaphragmatic screening and ultrasound scans were helpful in confirming the diagnosis.

All patients underwent surgical repair. The approach was through a laparotomy in 14, a thoracotomy in six, and a thoracoabdominal incision in two. The defect was sutured directly in 15 and patched with Dacron in three; the four eventrations were plicated. The eight patients with malrotation had a simultaneous Ladd's procedure. Postoperative chest drains were not used in 14 patients; two subsequently required one, one for a suspected tension pneumothorax (that was not confirmed) and one for a persistent pleural effusion.

Results

There were no serious postoperative complications and no deaths. Follow up ranged from 3 months to 3·5 years (median 6 months). Five patients who had failed to thrive improved immediately with weight gain increasing from below the third centile to above the 10th centile within two months of operation. The remaining two patients who had failed to thrive seemed to received no benefit. The patients with chronic respiratory and gastrointestinal symptoms all improved rapidly after operation. The three patients who had been dependent on ventilatory support were all successfully extubated within a week of operation.

Discussion

This series emphasises the varied presentation of congenital diaphragmatic defects diagnosed after the neonatal period. Chronic respiratory and gastrointestinal symptoms have been previously described.[1 2] Less than half of the patients in our series, however, had these symptoms. Failure to thrive was the commonest presentation, unlike the series described by Berman *et al* in which only one patient presented with failure to thrive.[2] This report is the first to our knowledge to emphasise that poor weight gain is a common presenting feature of congenital diphragmatic defects diagnosed after the neonatal period.

The association of group B β haemolytic streptococcal infection and late presenting diaphragmatic hernia (as occurred in four of our patients) has been previously described.[7–9] Graviss *et al* stated that the group B infection is not causally related to the development of a diaphragmatic hernia.[7] We postulate that compression of the lung with resultant consolidation may predispose the infant to this infection.

One of the factors contributing to diagnostic delay is a normal chest radiograph. Wiseman and MacPherson in 1977 coined the term 'acquired' congenital diaphragmatic hernia for lesions presenting at variable times after documented normal chest radiographs.[6] This contributed to the diagnostic delay in one of our patients. Two patients had abnormal chest radiographs at the referring hospital, but that on admission to this unit was normal. It would seem that the herniated abdominal contents can reduce spontaneously through the defect. The presence of a normal chest radiograph after one showing a diaphragmatic defect, therefore, does not preclude the diagnosis.

The risks of misdiagnosing right sided congenital diaphragmatic hernias as persistent pleural effusions in patients who cannot be weaned from a ventilator are stressed.[4 7] Various methods have been recommended to evaluate the integrity of the diaphragm. These include radionucleatide scanning of the liver and spleen, umbilical venography, computed tomography, contrast peritoneography, barium meal examination, diaphragmatic screening, and ultrasonography. Diaphragmatic screening is useful only in patients who are breathing spontaneously. Ultrasound scans and barium meal examinations are helpful in ventilated infants. A diaphragmatic defect should be suspected in every patient in whom the diaphragm is not clearly visible on radiography.

Further investigations aimed at establishing the presence of an intact diaphragm should therefore be undertaken. Keeping the possibility of the diagnosis in mind should avoid undue delay, misdiagnosis, and inappropriate treatment.

Three patients (23%) had Morgagni hernias. This is a higher incidence than the usually reported 1–2% of all congenital diaphragmatic hernias and reflects the fact that they can be small defects that are not usually detected at birth.[10] Booker *et al* reported a similarly high incidence of Morgagni hernias in older children.[3] The defects are usually right sided, as in our three cases, and lie anteriorly between the xiphisternum and costal muscle fibres of the diaphragm. Two of our patients had gastrointestinal symptoms (intermittent colicky abdominal pain and vomiting) and their hernias contained colon. The small defect increases the risks of strangulation, and in the two cases reported by Booker *et al* necrotic bowel was found.[3]

Once the diagnosis of a diaphragmatic defect has been established, surgical correction should be performed without delay. We plan operations for the next available routine list, which was usually a matter of days. Even with this policy one of our patients developed intestinal obstruction while waiting and required an emergency operation. We therefore recommend that all patients stay in hospital before operation, but emergency operation is not normally indicated. Other complications that have developed before operation include cardiorespiratory arrest[2] and intestinal infarction.[3 5]

Our approach to these late diagnosed diaphragmatic defects is as follows: a barium meal and follow through examination is carried out to exclude the presence of a malrotation. In patients without a malrotation we recommend a transthroacic approach to the repair of the defect. Patients with a malrotation require an abdominal approach to facilitate a simultaneous Ladd's procedure.

References

1 Bonham Carter RE, Waterston DJ, Aberdeen E. Hernia and eventration of the diaphragm in childhood. *Lancet* 1962;**i**:656–9.

2 Berman L, Stringer D, Ein SH, *et al.* The late presenting pediatric Bochdalek hernia: a 20 year review. *J Pediatr Surg* 1988;**23**:735–9.

3 Booker PD, Meerstadt PWD, Bush GH. Congenital diaphragmatic hernia in the older child. *Arch Dis Child* 1981;**56**:253–7.

4 Chilton HW, Chang HT, Jones MD, *et al.* Right-sided congenital diaphragmatic herniae presenting as pleural effusions in the newborn: dangers and pitfalls. *Arch Dis Child* 1978;**53**:600–3.

5 Wooley MM. Delayed appearance of a left posterolateral diaphragmatic hernia resulting in significant small bowel necrosis. *J Pediatr Surg* 1977;**12**:673–4.

6 Wiseman NE, MacPherson RI. 'Acquired' congenital diaphragmatic hernia. *J Pediatr Surg* 1977;**12**:657–65.

7 Graviss ER, Danis RK, Lewis JE, *et al.* Peritoneography diagnosis of delayed onset right-sided diaphragmatic hernias masquerading as pleural effusion. *J Pediatr* 1980;**97**:119–22.

8 Young LW, McClead RE, Graham M, *et al.* Radiological case of the month: postnatal appearance of diaphragmatic hernia. *Am J Dis Child* 1978;**139**:1137–8.

9 McCarten KM, Rosenberg HK, Borden S, *et al.* Delayed onset of right diaphragmatic hernia associated with group B streptococcal infection in the newborn. *Radiology* 1981;**139**:385–9.

10 Synder WH, Greaney EM. Congenital diaphragmatic hernia: 77 consecutive cases. *Surgery* 1965;**57**:576–88.

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Need for new reference curves for height

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SUMMARY Data from the National Study for Health and Growth, on children aged from 4·0 to 12·0 years measured in 1972, 1985, and 1986 were used to assess whether new growth standards are required, and which subgroups of children might require separate standards. The change over this period, from just over half a centimetre in the youngest girls to over a centimetre in the oldest boys, warrants the use of revised reference curves, which are also needed for Afro-Caribbean children.

The standards, or reference curves, currently used in the clinical assessment of a child's height or rate of growth are based on data that were collected in 1959, although they were updated in 1965.[1 2] Mean height of children aged 5 to 11 years increased in the 1970s,[3] although no further increase was seen from 1979 to 1986,[4] and Voss *et al* suggested that new growth charts are now required,[5] at least for the more affluent areas of southern England.

At an initial assessment a child's height will be assessed in relation to a reference group, and expressed as above or below some critical centile, such as the third. If the reference group is not representative of the population to which the children belong, the percentage of healthy children below the nominal third centile may differ from 3%. If it is less than 3%—for whatever reason—the screening process may be less sensitive than intended, and children may be excluded from follow up who would otherwise have been more fully investigated.

Trends over time and geographical variation are not the only reasons why new standards might be required. Rona and Chinn found children of Afro-Caribbean origin to be about 3·5 cm taller, and Gujarati speaking children to be about 3 cm shorter, than white children on average.[6] A screening procedure that used growth charts based on data from white children would therefore lack sensitivity for Afro-Caribbean children.

Goldstein and Tanner argued that there should be separate standards for subgroups of the population, and suggested standards conditional on sex, parental heights, family size, area of residence, and ethnic characteristics.[7]

The National Study for Health and Growth is a continuing surveillance study of children most of whom are aged from 5 to 11 years. Standards for attained height constructed from data collected in 1972 were found to be close to the Tanner standards.[8] Data on a comparable sample were available from the 1986 survey, and on ethnic minority and inner city children from 1985. The aim of this analysis was to ascertain whether new reference curves are required, and to assess the relative importance of the grouping variables suggested by Goldstein and Tanner.[7]

Subjects and methods

In 1972 the National Study for Health and Growth was carried out in 22 areas of England and six in Scotland, selected by stratified random sampling of employment exchange areas, and weighted towards poorer areas.[9] As far as possible areas and selected primary schools within areas remained in the study; when replacement was necessary either another school in the same area was selected or another area chosen from the same stratum. Trends in height for the 22 English areas from 1972 to 1986 were comparable with those for the 13 areas in which the same schools participated throughout,[4] but one area in Scotland was by chance replaced by an area in which children were substantially taller.

Areas were visited yearly until 1982, and every two years thereafter. In 1983 the design was modified. Schools in wards in 10 English inner city areas and in 10 areas containing a high proportion of children from ethnic minorities were added and surveyed in alternate years to the original schools.[6]

At the same time eight further Scottish areas were included, selected from the original sampling frame. Data for the original quasirepresentative English samples in 1972 and 1986, and for the new Scottish areas and the inner city and ethnic minority areas sample in 1985, have been analysed.

In 1985 the children were classified as white, Afro-Caribbean, Urdu, Gujarati, Punjabi, other Asian, and others, according to the fieldworker's assessment and the language spoken at home.[6] The few non-white children measured in 1972 were omitted from analysis, as the language spoken at home was not known. Non-white children in the 1986 English sample, and from Scotland, were omitted for the same reason. This eliminated a substantial number of children in just one English area, which had replaced one of the 22 original areas in 1982. Data for children from the original Scottish area and the current non-comparable area that replaced it were omitted completely, so that data were used from five Scottish areas in 1972 and in 1986, and from eight in 1985. The latter eight areas were grouped with the 1986 areas rather than the 1985 English areas because of comparability of method of selection.

The areas selected as inner city areas on the basis of overcrowding, shared amenities, and high rates of unemployment tended to have a higher than average proportion of ethnic minorities, and conversely those selected as Asian or Afro-Caribbean areas tended to have at least one feature of inner city areas. All 20 areas are therefore referred to in the following as inner city areas.

Height was measured on a specially designed stadiometer (Holtain) using the method described by Tanner *et al*[1 2] and recommended by Weiner and Lourie for the International Biological Programme.[10] The measurements were made by a school nurse supervised by a trained fieldworker who made an additional quality control measurement on about one in 10 children. Height was recorded to the last complete 0·5 cm on the scale in 1972, and to the last 0·1 cm in 1985 and 1986; 0·25 cm or 0·05 cm was added to each measurement as appropriate.

As the between child variance of height increases with age, in order to analyse data for all ages a standard deviation (SD) score was calculated for each child,[11] which was the difference between the child's height and the mean for its age and sex, divided by the age and sex specific standard deviation. Use of the SD score has the additional advantage of immediate conversion to centile score, as height is known to be a normally distributed variable. The means and standard deviations were obtained from 1972 English data by smoothing values calculated from six month age groups. Standard deviations were first adjusted for age grouping as described by Healy,[12] and means and standard deviations each smoothed using cubic polynominal curves for boys and girls separately. Children outside the age range 4·0 to 12·0 years were excluded, as were those for whom height was not recorded.

Data on the number of children in the family, father's social class, the child's birth weight, and the heights of the parents were obtained from a self administered questionnaire that was usually completed by the child's mother. In 1972 questions concerning social class and parental height referred to 'respondent' and 'spouse' rather than to child's mother and father; therefore there were 'missing' data when the respondent was other than the mother or father. In 1985 and 1986, questions

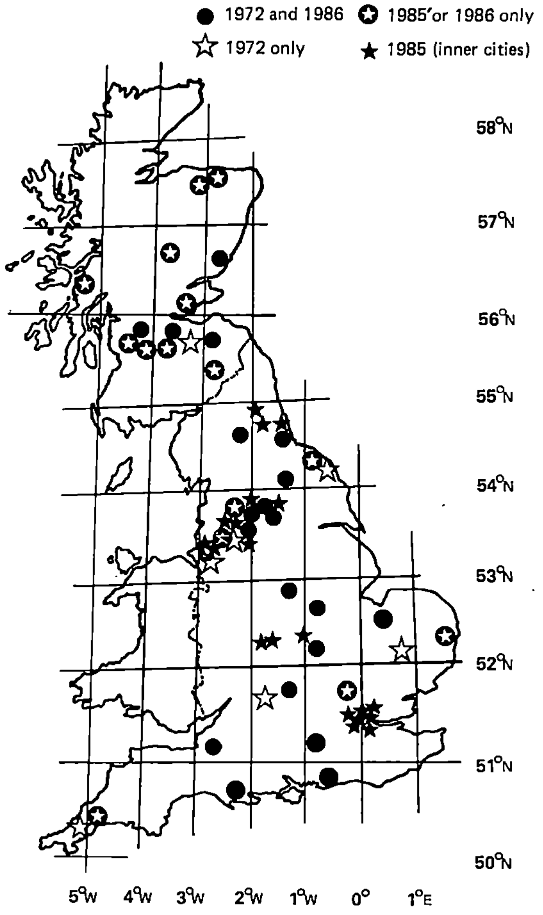

Fig 1 *Areas in the National Study for Health and Growth. Changes of school within areas are not shown.*

referred to child's father or male guardian for social class, and to natural mother and father for heights of parents. Family size and father's social class were treated as categorical variables with a missing value category. Birth weight and heights of parents were analysed as continuous variables. Children with missing data were included in the analysis, and mean differences in height SD scores were estimated between children with missing data and those with an average birth weight, mother's height, or father's height.

So that results relating to area of residence would be in a usable form, each National Study for Health and Growth area was assigned its latitude and longitude to the nearest degree (fig 1). Multiple regression analyses were carried out with height SD score as the dependent variable. The independent variables included year group (table 1), accounting for trend over time and inner city selection, and ethnic origin with categories as in table 2, family size (table 3), social class (table 4), country (England and Scotland); the continuous variables were birth weight, mother's height, father's height, and latitude and longitude.

SD scores based on the Tanner standards were also calculated so that adjustments to these could be calculated. The published means and standard deviations were interpolated by age using cubic and quartic polynomials respectively.[1] [2]

Results

The number of boys and girls in each age group for the total 1972 sample, the 1985 English inner city sample, and the Scottish sample for 1985 combined with the total 1986 sample are shown in table 1. Numbers of children in school fell between 1972 and 1986,[4] but the eight extra Scottish areas that took part in 1985 compensated for the decrease. Table 2 shows the distribution of children in the 1985 English inner city sample by ethnic group. All Asians outnumbered white children, but the latter was the largest group in the inner city sample, followed by the Punjabi speaking Asians.

Table 2 *Percentage distribution of children by ethnic group in the National Study for Health and Growth in the English inner city areas in 1985*

	Boys	*Girls*
White	37·2	35·8
Afro-Caribbean	13·4	14·9
Asian:		
Urdu	8·0	9·4
Gujarati	9·4	8·2
Punjabi	20·6	19·6
Other	4·4	4·1
All other	7·1	7·9
Total No of children	3304	3216

Table 1 *Distribution of children by age and sex in the National Study for Health and Growth in the quasirepresentative samples in 1972 and 1985/86 and in the English inner city areas in 1985*

Age group (years)	*Boys*			*Girls*		
	1972 England and Scotland	*1985 England (inner city)*	*Scotland 1985 and England and Scotland 1986*	*1972 England and Scotland*	*1985 England (inner city)*	*Scotland 1985 and England and Scotland 1986*
4–<5	120	122	168	123	99	132
5–<6	721	535	769	715	492	687
6–<7	754	472	831	714	503	708
7–<8	802	507	766	777	441	707
8–<9	740	447	700	708	477	650
9–<10	780	447	703	680	444	647
10–<11	743	451	751	730	466	733
11–<12	434	323	480	413	294	469
Total	5094	3304	5168	4860	3216	4733

Table 3 shows the distribution of children by family size in each of the three samples. Average family size decreased between 1972 and 1986, confirmed by the previous analysis of areas continuing in the study.[4] Despite the greater proportion of missing data, family size was found to be greater in the inner city areas sample, particularly among Asian groups.

Table 4 shows the distribution of children by father's social class. There was a shift from manual

Table 3 *Percentage distribution of children by size of family in the National Study for Health and Growth in the quasirepresentative samples in 1972 and 1985/86 and in the English inner city areas in 1985*

No of children in family	*Boys*			*Girls*		
	1972 England and Scotland	*1985 England (inner city)*	*Scotland 1985 and England and Scotland 1986*	*1972 England and Scotland*	*1985 England (inner city)*	*Scotland 1985 and England and Scotland 1986*
1	6·6	6·4	8·4	6·4	6·3	8·5
2	30·2	19·2	46·8	30·1	18·8	45·8
3	24·4	21·1	24·5	25·1	17·8	24·4
4	14·1	13·2	7·9	13·0	14·4	9·4
5	7·2	8·4	2·3	7·1	8·8	2·4
6	2·8	4·6	1·0	3·2	5·1	1·0
7	1·2	1·7	0·5	1·7	2·5	0·3
8 or more	1·5	2·0	0·1	1·8	2·0	0·1
Not known	12·0	23·4	8·5	11·7	24·3	7·9
Total No of children	5094	3304	5168	4860	3216	4733

Table 4 *Percentage distribution of children by father's social class in the National Study for Health and Growth in the quasirepresentative samples in 1972 and 1985/86 and in the English inner city areas in 1985*

Father's social class	*Boys*			*Girls*		
	1972 England and Scotland	*1985 England (inner city)*	*Scotland 1985 and England and Scotland 1986*	*1972 England and Scotland*	*1985 England (inner city)*	*Scotland 1985 and England and Scotland 1986*
I	3·5	0·8	5·0	3·4	1·0	4·0
II	11·2	5·6	20·9	10·7	4·9	20·0
III non-manual	7·2	2·7	6·6	6·7	2·7	7·6
III manual	35·6	23·9	33·2	34·8	24·9	32·1
IV	10·2	15·5	9·5	10·9	14·6	11·1
V	4·8	5·1	2·9	4·7	4·7	3·1
Armed forces and unclassifiable	6·0	0·7	0·9	6·1	0·4	0·8
No father in home	4·6	15·8	10·1	4·5	15·8	10·3
Not known	16·8	29·8	10·9	18·1	31·0	11·1
Total No of children	5094	3304	5168	4860	3216	4733

to non-manual occupations, especially to those in social class II, between 1972 and 1986. This was in line with national trends from 1971 and 1981.[13] The inner city sample had a higher proportion of semiskilled fathers, and almost certainly a lesser proportion in non-manual and skilled occupations, but conclusions were hampered by the large amount of missing data. In addition there was a higher proportion of single parent (mother) families, greater in the Afro-Caribbean group. There was a rise in one parent families in the quasirepresentative sample from 1972 to 1986.

Only a small number of children (five boys and seven girls) had a height SD score greater than 4 or less than −4. These were omitted as they were thought to be erroneous. There was then a total of 13 561 boys and 12 802 girls measured at one of three surveys and included in the multiple regression analyses.

Father's social class was reduced to the categories non-manual, manual, and not known, with no significant increase in the residual sum of squares, and a worthwhile simplification was achieved by grouping family size into the six categories 1, 2, 3, 4 or 5, 6 or more, or not known.

All the variables in the analysis, with family size and father's social class modified as above, were independently significantly associated with height SD score except for the missing value adjustment for father's height for longitude for boys and for father's social class, and the adjustment for missing birth weight for girls. Almost all were highly signficant associations ($p<0{\cdot}001$).

Table 5 gives the estimated effect on height SD score independently attributed to each of the factors in the multiple regression model. The column on the left for both boys and girls, gives the difference for each variable or category from a white child measured in 1972, with no siblings, father in non-manual occupation, birth weight 3380 g, mother's height 160 cm, father's height 176·5 cm, and living near 50°N 5°W. The column on the right for both boys and girls, gives the corresponding figures when only the biological variables (ethnic origin, birth weight, and parental heights) and sample selection and trend over time are taken into account. This table is given primarily to illustrate the importance of each factor, but can also be used to calculate an expected height SD score, as illustrated in table 6 for two rather extreme cases.

This is not to say that either such child exists. The 'total' line gives SD score in units applicable to all children, as non-conditional standards have generally been calculated. As the factors in the left hand column in table 5 account for about 23% of the variation, however, it is necessary to judge a child against the variation around his or her group mean to use the table to provide a proper conditional height SD score. By dividing by the residual within group standard deviation, which is less than one SD score in the above units, a conditional SD score is obtained. The final line of table 5 gives the necessary divisor, which gives the final SD score. If the first child was 7·8 years old and 123·9 cm tall, and so at the 50th centile (nominal SD score=0·0) as judged by the Tanner standards[1 2] or Rona and

Table 5 *Estimated difference in height SD scores from a white child measured in 1972, with no siblings, father in non-manual occupation, birth weight 3380 g, mother's height 162 cm, father's height 176·5 cm, and living in Cornwall (50°N 5°W)*

	Boys		*Girls*	
	Full adjustment	*Partial adjustment (as shown)*	*Full adjustment*	*Partial adjustment (as shown)*
Ethnic origin:				
Afro-Caribbean	0·62	0·64	0·75	0·80
Urdu	0·05	−0·05	0·24	0·14
Gujurati	0·14	0·10	0·01	−0·04
Punjabi	0·23	0·16	0·30	0·23
Other Asian	0·26	0·24	0·21	0·19
Other	0·15	0·21	0·31	0·36
Family size: 2	−0·09	Not adjusted	−0·13	Not adjusted
3	−0·22	Not adjusted	−0·20	Not adjusted
4 or 5	−0·32	Not adjusted	−0·31	Not adjusted
6 or more	−0·47	Not adjusted	−0·50	Not adjusted
not known	−0·16	Not adjusted	−0·22	Not adjusted
Father's social class:				
Manual	−0·04	Not adjusted	−0·01	Not adjusted
Not known	−0·10	Not adjusted	−0·03	Not adjusted
Increase/1000 g of birth weight	0·33	0·32	0·33	0·32
Adjustment for missing birth weight	−0·07	−0·08	−0·05	−0·08
Increase/10 cm of mother's height	0·43	0·44	0·41	0·42
Adjustment for missing mother's height	−0·16	−0·17	−0·20	−0·22
Increase/10 cm of father's height	0·35	0·37	0·31	0·32
Adjustment for missing father's height	−0·04	−0·07	0·01	0·00
Increase/degree latitude north	−0·02	Not adjusted	−0·03	Not adjusted
Increase/degree longitude west	−0·01	Not adjusted	−0·02	Not adjusted
Scotland	0·10	Not adjusted	0·19	Not adjusted
Inner city sample	−0·02	0·02	−0·05	−0·05
1986 or Scotland 1985 (secular trend)	0·06	0·11	0·03	0·08
Mean to which differences should be added	0·34	0·09	0·33	0·12
Final divisor*	0·89	0·90	0·88	0·89

*See text.

Table 6 *Two examples of expected height SD score calculation using the full adjustment estimates from table 5*

	First child		*Second child*	
	Child's data	*Contribution to expected SD score*	*Child's data*	*Contribution to expected SD score*
Sex	Female	Not applicable	Male	Not applicable
Ethnic origin	Afro-Caribbean	+0·75	White	Not applicable
Family size	1	Not applicable	6	−0·47
Father's social class	Non-manual	Not applicable	Manual	−0·04
Birth weight	4380 g	+0·33	2380 g	−0·33
Mother's height	172 cm	+0·41	157 cm	−0·215
Father's height	181·5 cm	+0·155	166·5 cm	−0·35
Latitude	51°N	−0·03	55°N	−0·10
Longitude	0°	+0·10	3°W	+0·02
Country	England	No applicable	England	Not applicable
Inner city	Yes	−0·05	No	Not applicable
Year	1985	Not applicable	1986	+0·06
'Mean'	0·33	0·33	0·34	0·34
Total		1·995		−1·085
Final divisor*	0·88		0·89	

*See text.

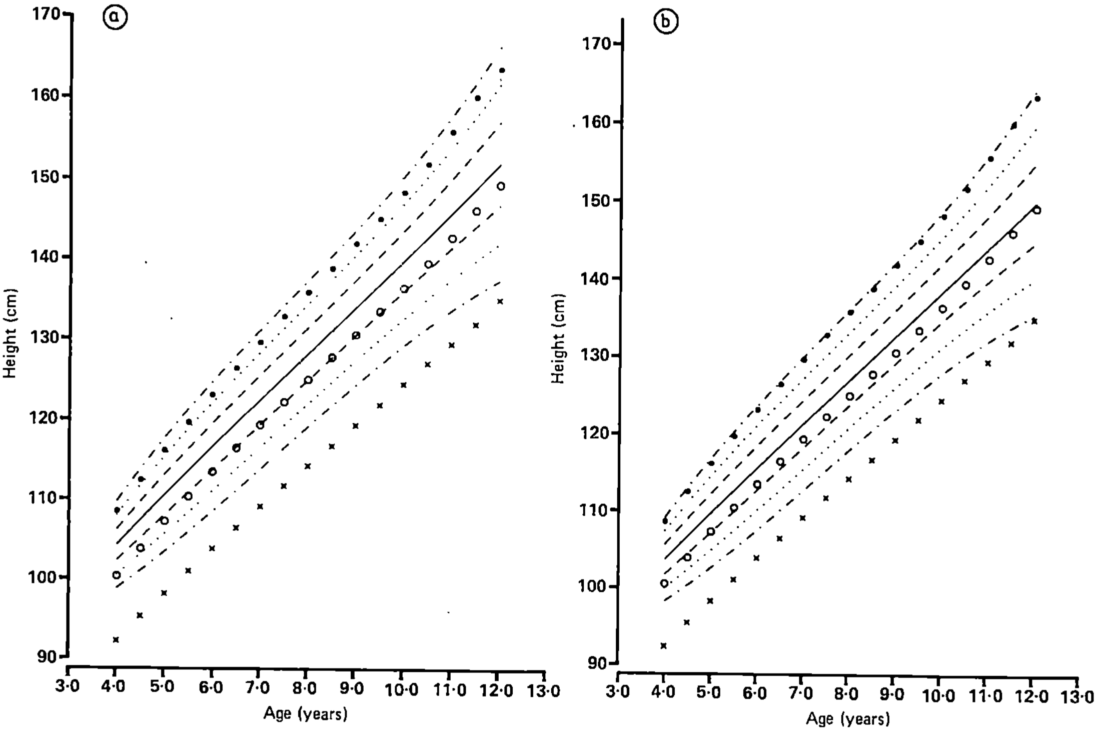

Fig 2 *Comparision of 1986 reference centiles (3rd, 10th, 25th, 50th, 75th, 90th, 97th) for two white girls: birth weight 3380 g, mother's height 162 cm, father's height 176·5 cm, with no siblings, and father in non-manual occupation; (a) living near 51°N 1°E and (b) living near 55°N 3°W. Centiles: 3rd and 97th —·—; 10th and 90th ·····; 25th and 75th – – –; and 50th ———. Tanner 3rd (×), 50th (○), and 97th (●) centiles.*

Altman,[8] then she would have a conditional SD score of −2·27, which is a little above the 1st centile. If of nominal SD score (1·0), then her conditional SD score would be (1–1·995)/0·88=−1·13, which is just above the 10th centile.

Table 5 (left hand columns) show that ethnic origin, family size, birth weight, and heights of parents may be of considerable importance in the assessment of a child, but that social class and trend over time are of little importance when these other factors have been taken into account. The columns on the right, in comparison, show that birth weight and parental height adjustments are stable, but that ethnic origin adjustments depend on the other variables in the analysis, the differences being mainly due to the omission of family size in these columns.

The maximum effect of area of residence in England, from the south east at 51°N 1°E to the north west at 55°N 3°W was 0·15 SD score for boys and 0·22 SD score for girls, and is shown for girls in fig 2; estimated from the rounded figures in table 5 the effect was 0·12 and 0·20 SD score, respectively. Each of these centile lines is for a white child with no siblings, father in non-manual occupation, and with average birth weight and parental heights. They have been adjusted for the secular trend; the Tanner 3rd, 50th, and 97th centiles are shown for comparison. The centile curves in fig 2 are closer together than the Tanner centiles because they are each given for fixed values of the biological and social variables.

The mean adjustment for secular trend to the unconditional Tanner standards for white children was estimated to be 0·20 SD score for boys and girls. Variation in heights of white children was reduced, so that the adjusted Tanner SD score should then be divided by 0·93 for boys, and 0·92 for girls, in order to retain a standard deviation of 1·0. The net result is of little change in the 97th centile, but a substantial increase in the 3rd centile. The adjustments are not entirely independent of age, however, as they represent a mean change ranging from just over half a centimetre in the youngest girls to over a centimetre in the oldest boys.

Discussion

Standards for height are required for the assessment of short stature, and, to a lesser extent, tall stature. Failure of growth may have various causes, of which the most important are chronic disorders including endocrine conditions amenable to treatment, and social and psychological problems. Recently treatment with growth hormone was shown to be effective for 'short normal' children,[14] although the outcome for final height is unknown. Most tall children do not suffer from any pathological condition, but treatment may be sought to prevent embarrassment. Whatever the eventual diagnosis and intervention (if any), the immediate presenting problem is the same, that of the initial assessment of the height of the child in relation to his or her age group as a whole, and in comparison with whatever subgroup is most appropriate. It is with the initial assessment that this paper is concerned, and not with follow up assessments for which height velocity standards,[1 2] longitudinal standards,[15] or previous height conditional standards,[16] should be used.

The primary aim is therefore to minimise delay in treatment or intervention for those for whom it is appropriate, although large numbers of unnecessary referrals to paediatric clinics or follow up appointments are also undesirable. The cut off point below which a child is referred or followed up should therefore maximise detection of treatable conditions, or some suitable combination of sensitivity and specificity. To optimise the cut off point or estimate the delay in intervention for those not followed up, however, we would need to know the eventual diagnosis for a large number of children. This has a bearing on the question of adjustment for the trend over time and on what factors should be taken into account.

Only information likely to be available when a child is first assessed has been considered in this analysis. Of the variables included, ethnic origin, birth weight, and heights of parents are each independently associated with a child's height to a sufficient extent to require consideration, and when combined should adjust for genetic potential. Secular trend is of relatively little importance, especially if family size is also taken into account. The relation between height and latitude and longitude is sufficient that separate standards for England (north west), England (south east), and Scotland also require consideration. Social class has relatively little effect, but family size is important if it is thought appropriate to take social factors into account. Unfortunately there was some suggestion that the relation of height to family size is associated with ethnic origin, so this is not straightforward.

The significance of the relationship of any factor to height does not automatically imply, however, that it should be taken into account in the assessment. If at a given height Afro-Caribbean children have the same prevalence of treatable conditions, then their overall prevalence will be lower and it is appropriate to use reference curves for white children. In the absence of diagnostic data, however, we must presume that Afro-Caribbean children have a similar prevalence to others and therefore greater prevalence at a given height, and that use of standards for white children would cause delay in intervention for those for whom it is appropriate.

It is also reasonable to assume that the prevalance of treatable problems has not decreased over time, so that the trend in height over time requires new unconditional standards for white children.

The difference in mean height SD score of 0·5 between singleton children and those in families of six or more is considerable, but whether it is associated with corresponding differences in the incidence of treatable causes of short stature (which argue against adjustment for family size) is unknown. Information about father's social class is often unobtainable or inappropriate for inner city children, and of small importance among these data when other factors were taken into account.

In the absence of outcome data to optimise cut off points for use in screening there are three possible strategies. One is to use the same reference curves for all children basing them on data representative of the whole population on the assumption that height differences between groups reflect differences in the prevalence of treatable conditions. In effect this has been the policy when the unconditional Tanner standards have been used alone. The second is to use conditional standards, and the third is to use standards appropriate to the most advantage group in the belief that these represent the optimal growth that should be the target for all. The first and third strategies may differ in the cut off points actually used, but they do not differ fundamentally. Goldstein and Tanner argued cogently against the third, and in favour of the second strategy on several grounds.[7] They believed that differences from environmental causes should be treated in groups, and that individual subjects should be screened with standards derived from children of similar genetic background and environment. They recommended subgroups defined in terms of sex, family size, place of residence, ethnic origin, and heights of parents, to which birth weight should be added if their argument is accepted. We accept their argument for genetic effects, but not for environmental ones.

It should be noted that at present conditioning on birth weight and parental heights does not eliminate differences between ethnic groups, although these can be expected to diminish over time. In this limited age range, however, they could reflect differences in age at maturation between ethnic groups.

If unconditional reference curves are required the trend over time is such that revision of the Tanner standards is required. Our minimum estimate of trend between 1972 and 1986 for white children from the 1972 based SD score, was 0·17 for boys and 0·12 for girls, or up to about 1·2 cm in older boys, and a minimum of 0·6 cm in younger girls. The trend is greater if estimated from the approximate Tanner SD score. The possible delay in treatment of Afro-Caribbean children from the use of standards for white children is undesirable. The National Study for Health and Growth can provide data for only 4 to 12 years, and extrapolation of the trends to other ages should not be assumed. Opposite trends in height in infants and older children have been reported from The Netherlands.[17] At a minimum, revised standards are required for white and Afro-Caribbean children across the whole age range for growth.

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References

[1] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity in British children 1965. *Arch Dis Child* 1966;**41:** 454–71.

[2] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maternity for height, weight, height velocity and weight velocity in British children 1965. *Arch Dis Child* 1966;**41:** 613–35.

[3] Chinn S, Rona RJ. The secular trend in the height of primary school children in England and Scotland from 1972–1980. *Ann Hum Biol* 1984;**11:**1–16.

[4] Chinn S, Rona RJ, Price CE. The secular trend in height of primary school children in England and Scotland 1972 to 1979 and 1979 to 1986. *Ann Hum Biol* (in press).

[5] Voss LD, Wilkin TJ, Betts PR. Do we need new growth charts? *Lancet* 1987;ii:447–8.

[6] Rona RJ, Chinns S. National Study for Health and Growth: social and biological factors associated with height of children from ethnic groups living in England. *Ann Hum Biol* 1986;**13:** 453–71.

[7] Goldstein H, Tanner JM. Ecological considerations in the creation and the use of child growth standards. *Lancet* 1980;**i:** 582–5.

[8] Rona RJ, Altman DG. National Study for Health and Growth. Standards of attained height, weight and triceps skinfold in English children 5 to 11 years old. *Ann Hum Biol* 1977;**4:** 501–23.

[9] Irwig LM. Surveillance in developed countries with particular reference to child growth. *Int J Epidemiol* 1976;**5:**57–61.

[10] Weiner JS, Lourie JA. *Human biology, a guide to field methods.* International Biological Programme Handbook No 9. Oxford: Blackwell Scientific Publications, 1969.

[11] Rona RJ, Swan AV, Altman DG. Social factors and height of primary school children in England and Scotland. *J Epidemiol Community Health* 1978;**32:**147–54.

[12] Healy MJR. The effect of age-grouping on the distribution of a measurement affected by growth. *Am J Phys Anthropol* 1962;**20:**47–50.

[13] Beacham R. Economic activity: Britain's workforce 1971–81. *Population Trends* 1985;**37:**6–14.

[14] Hindmarsh PC, Brook CGD. Effect of growth hormone on short normal children. *Br Med J* 1987;**295**:573–7.

[15] Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, and stages of puberty. *Arch Dis Child* 1976;**51**:170–9.

[16] Cameron N. Conditional standards for growth in height of British children from 5·0 to 15·99 years of age. *Ann Hum Biol* 1980;**7**:331–7.

[17] Roede MJ, van Wieringen JC. Growth diagrams 1980. *Tijdschrift voor Sociale Gezondheidszong* 1985;**63**(suppl):1–34.

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Growth and body proportions in congenital adrenal hyperplasia

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SUMMARY Total height, sitting height, and subischial leg length were measured in 27 patients (19 girls and eight boys aged 4·3–21·1 years) with congenital adrenal hyperplasia to determine the influence of chronic hyperandrogenaemia on body proportions. Proportions were normal in 24 patients with classical congenital adrenal hyperplasia who had received steroid treatment since birth, but one of three patients with non-classical (late onset) congenital adrenal hyperplasia had a disproportionately large trunk. Eleven patients with classical congenital adrenal hyperplasia had completed growth, of whom seven had height standard deviation (SD) scores for chronological age less than zero, and one had extremely short stature (SD score −3·25). In 13 patients who were still growing, nine had height SD scores for chronological age of less than zero despite having mean (SD) advances in bone age over chronological age of 1·64 (1·68) years. Height SD scores for bone age were less than 0 in all 13 patients, indicating a loss of height despite advanced skeletal maturation.

Doses of glucocorticoid that permit mild chronic or intermittent hyperandrogenaemia also seem to be associated with mild growth retardation. An adult height below average may be an inevitable consequence for many patients with congenital adrenal hyperplasia receiving conventional glucocorticoid treatment.

Growth in stature is an important component in assessing the outcome of treatment in patients with congenital adrenal hyperplasia. Growth velocity provides a valuable guide to the adequacy of control during infancy and childhood, and the attainment of normal adult height is a principle aim of treatment.[1] Though this may sometimes occur without treatment,[2] diminished final height as a result of premature epiphyseal fusion caused by chronic hyperandrogenaemia is the usual outcome in untreated congenital adrenal hyperplasia.[3] Below average final height is common even with treatment[3 4]; this may result from mild or intermittent hyperandrogenaemia associated with inadequate adrenal suppression, or from the direct growth suppressive effect of excessive treatment with glucocorticoids.[5 6]

Increased plasma concentrations of testicular testosterone in boys and adrenal androgens in girls contribute to the adolescent growth spurt, mainly through their effect on truncal growth.[7 8] Precocious puberty is characterised by a decrease in final height, but a disproportionate increase in the size of the trunk.[9] Hyperandrogenaemia in congenital adrenal hyperplasia is present from early fetal life, and to a variable extent postnatally depending on both the age at diagnosis and the degree of therapeutic control. Inadequate control can lead to pseudoprecocious puberty in boys and true precocious puberty in both sexes.[1] These factors suggest that growth may be disproportionate in congenital adrenal hyperplasia. This paper reports the first systematic study of growth and body propor-

Table 1 *Classification of patients according to type of congenital adrenal hyperplasia*

	Classical adrenal hyperplasia		*Non-classical adrenal hyperplasia (group 3)*	*Total*
	Group 1 (complete growth)	*Group 2 (incomplete growth)*		
Boys	3	5	0	8
Girls	8	8	3	19
Total	11	13	3	27

Table 2 *Auxological data*

Case No	*Height (cm)*	*Sitting height (cm)*	*Subischial leg length (cm)*	*Chronological age (years)*	*Bone age (years)*	*Bone age minus chronological age*	*Chronological age*			*Bone age*			*F**
							Height SD score	*Sitting height SD score*	*Subischial leg length SD score*	*Height SD score*	*Sitting height SD score*	*Subischial leg length SD score*	
Group 1:													
1	153·9	82·2	71·7	18·3	Adult	—	−1·38	−1·72	−0·72	−1·38	−1·77	−0·72	−1·05
2	151·5	80·5	71·0	13·2	Adult	—	−0·88	−0·97	−0·51	−1·78	−2·32	−0·90	−0·46
3	158·5	87·1	71·4	14·0	Adult	—	−0·35	0·27	−0·71	−0·62	−0·19	−0·79	0·98
4	159·7	88·7	71·0	17·9	Adult	—	−0·42	0·32	−0·90	−0·42	0·32	−0·90	1·22
5	156·0	88·6	69·4	20·7	Adult	—	−1·03	−0·35	−1·30	−1·03	−0·35	−1·30	0·95
6	136·9	76·4	60·5	20·3	Adult	—	−4·22	−3·65	−3·59	−4·22	−3·65	−3·59	−0·06
7	167·8	87·3	80·5	21·1	Adult	—	0·93	−0·13	1·54	0·93	−0·13	1·54	−1·67
8	152·1	84·2	67·9	16·5	Adult	—	−1·68	−1·13	−1·69	−1·68	−1·13	−1·69	0·56
9	184·0	97·6	86·4	14·8	Adult	—	2·32	2·44	1·60	1·40	1·24	1·24	0·84
10	175·6	94·9	80·7	16·8	Adult	—	0·20	0·65	−0·08	0·14	0·04	−0·12	0·73
11	168·7	90·3	78·4	20·3	Adult	—	−0·90	−0·97	−0·67	−0·90	−0·97	−0·67	−0·30
Group 2:													
12	91·5	52·8	38·7	3·9	4·0	0·1	−2·07	−2·44	−1·02	−2·07	−2·44	−1·02	−1·42
13	143·4	76·5	66·9	12·0	13·7	1·8	−1·02	−0·87	−0·79	−2·55	−2·78	−1·82	−0·08
14	157·7	84·0	73·7	14·8	15·3	0·6	−0·70	−0·93	−0·19	−0·73	−1·06	−0·21	−0·74
15	155·7	81·0	74·7	13·6	13·7	0	−0·53	−1·29	0·23	−0·53	−1·29	0·23	−1·52
16	115·2	64·5	50·7	8·1	8·6	0·5	−1·71	−1·49	−1·41	−2·17	−1·84	−1·82	−0·08
17	142·7	76·7	66·0	15·7	15·3	−0·4	−3·25	−3·49	−2·18	−3·23	−3·44	−2·18	−1·31
18	155·0	83·3	71·7	13·0	14·2	1·3	−0·30	−0·15	−0·33	−0·93	−0·98	−0·67	0·18
19	149·0	82·2	66·8	12·9	15·3	2·5	−1·30	−0·47	−0·51	−2·04	−1·69	−1·97	0·04
20	96·5	57·8	38·7	4·3	3·6	0·7	−1·19	−0·91	−1·90	−0·34	0·09	−0·72	0·99
21	123·8	68·6	55·2	5·8	11·3	5·5	1·79	1·59	1·26	−2·86	−2·46	−2·88	0·33
22	112·5	62·5	50·0	5·4	9·0	3·7	0·21	−0·38	0·66	−3·18	−3·33	−2·72	−1·04
23	162·3	86·2	76·1	13.6	16.6	3.0	0·90	1·16	0·58	−1·69	−1·84	−1·17	0·58
24	117·4	67·5	49·9	5·2	7·4	2·2	1·92	2·02	0·96	−1·06	−0·35	−1·51	1·06
Group 3:													
25	151·7	85·0	66·7	12·7	Adult	—	−0·85	0·64	−1·46	−1·75	−0·65	−1·95	2·10
26	148·9	79·3	69·6	12·3	13·5	1·20	−0·10	−0·39	−0·33	−1·63	−1·79	−1·08	−0·06
27	111·6	62·9	48·7	5·6	8·8	3·24	0·03	0·00	0·39	−3·23	−2·61	−2·71	−0·39

*F=function—sitting height SD score (chronological age) minus subischial leg length SD score (chronological age).

tions in a group of patients with congenital adrenal hyperplasia.

Patients and methods

Twenty seven patients (19 girls and eight boys aged between 4·3 and 21·1 years) with congenital adrenal hyperplasia were studied. All had 21-hydroxylase deficiency except for one (case 12) who had 11β-hydroxylase deficiency. Patients were classified into three groups according to the type of congenital adrenal hyperplasia and their stage of growth (table 1). Groups 1 and 2 had received steroid treatment since infancy, initially as hydrocortisone 15–20 mg/m^2/day in divided doses, and later in adolescence as dexamethasone 0·25-0·75 mg/day in single or divided doses. Glucocorticoid doses were adjusted individually according to measurements of plasma and saliva adrenal androgens and 17-hydroxyprogesterone concentrations that were determined at periodic clinic visits, and regular assessments of growth velocity and bone age.[1] Treatment adjustments were made more recently using daily steroid profiles as an additional measurement.[10] There were three patients in group 3 with non-classical (late onset) congenital adrenal hyperplasia. One (case 25) was untreated at the time of the study, case 27 had been treated for less than three months, and case 26 had received hydrocortisone for five years.

Total height and sitting height were measured in each patient by the same observer (JR) using a Harpenden stadiometer and sitting height table. Subischial leg length was calculated by subtracting sitting height from height. Standard deviation (SD) scores for height and subischial leg length were calculated for chronological age and bone age using published tables.[11] [12] Bone age was determined by a single observer (JR) according to the Tanner-Whitehouse method.[13]

Results

Data on growth and bone age for the three groups are shown in table 2.

BONE AGE

All the patients in group 1 had completely fused epiphyses consistent with an adult bone age. Bone age was in advance of chronological age in all but one patient in group 2. The mean (SD) increase (bone age−chronological age) was 1·6 (1·7) years, indicating mild chronic hyperandrogenaemia. All

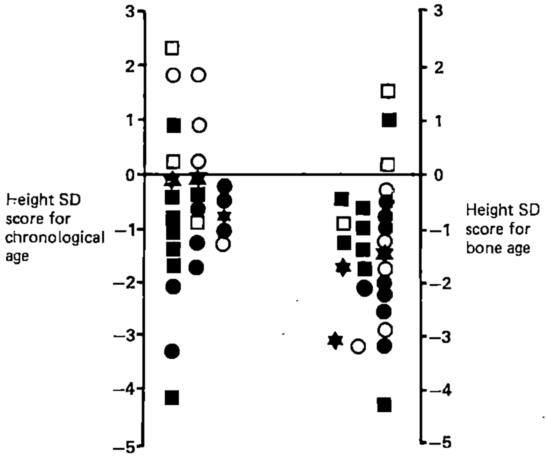

Fig 1 *Height SD scores, for chronological age and bone age, for the three groups. Solid symbols=girls, open symbols=boys, asterisks=late onset cases.*

three patients with late onset congenital adrenal hyperplasia (group 3) had advanced bone ages, and case 25 had attained adult maturity.

HEIGHT

Fig 1 shows height SD scores for both chronological and bone ages for all patients. Only three patients in group 1 had height SD scores for chronological age greater than zero; the mean (SD) score for this group, who had completed their growth, was −1·69 (1·56). Parental heights were available for only seven patients in this group; the mean paternal height (172·4 cm) and maternal height (166·1 cm) were not significantly different from the normal population.

Four patients in group 2 had height SD scores for chronological age greater than zero. When height SD score was calculated according to bone age, however, the scores were all less than zero indicating a considerable loss of height for the degree of skeletal maturity.

All the patients in group 3 had normal height SD scores for chronological age, but case 25 (whose epiphyses had already fused) will be a short adult. Height SD scores for bone age were all negative.

BODY PROPORTIONS

SD scores for sitting height and subischial leg length for all patients are shown in fig 2 (for chronological age and fig 3 (for bone age). The degree of proportionality of a subject may be assessed by comparing these values; in a perfectly proportioned individual the values will be equal even though the actual measurements may differ. This is indicated by the diagonal lines in figs 2 and 3 and the line of perfect proportionality in fig 4. In a healthy population the difference between the values, which may be expressed as the function—sitting height SD

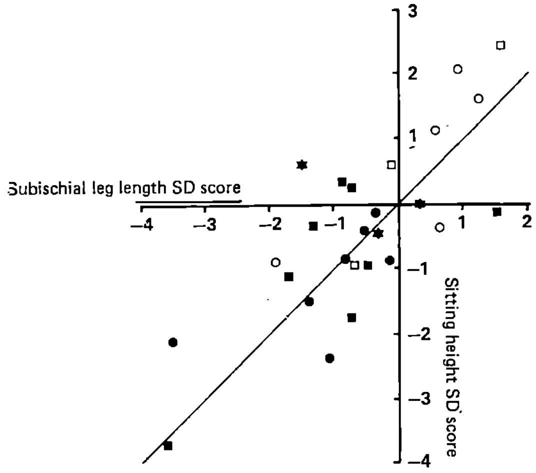

Fig 2 *Body proportions expressed as SD scores for sitting height and subischial leg length according to chronological age. Solid symbols=girls, open symbols=boys, asterisks=late onset cases.*

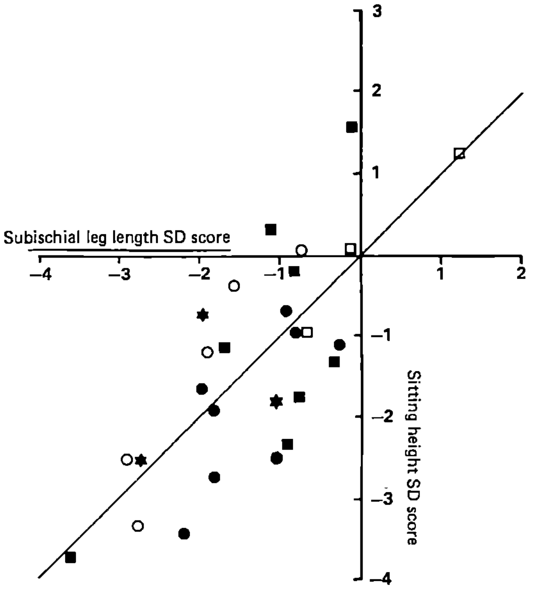

Fig 3 *Body proportions expressed as SD scores for sitting height and subischial leg length according to bone age. Solid symbols=girls, open symbols=boys, asterisks=late onset cases.*

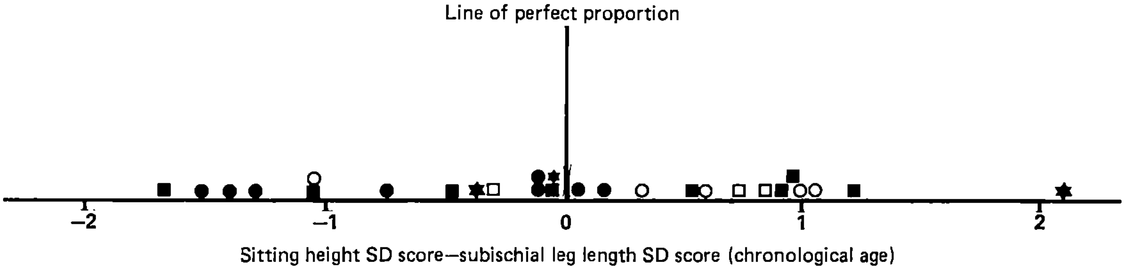

Fig 4 *Differences between sitting height SD scores and subischial leg length SD scores for all patients. Solid symbols=girls, open symbols=boys, asterisks=late onset cases.*

score for chronological age minus the subischial leg length SD score for chronological age—would have a normal distribution with a mean of zero and standard deviation of 1. Disproportionality, implying an abnormal association between trunk and leg length, might therefore be defined as a function score of more than +2 or less than −2. Sitting height SD scores and subischial leg length SD scores were generally reduced (negative), especially for bone age, and the impression that the values for patients in all three groups were scattered equally around the diagonal line (figs 2 and 3), was confirmed by the symmetrical distribution of function scores about the zero point, with a mean (SD) value for all patients of 0·02 (1·00) (fig 4). Similar results were obtained when each group was analysed separately. Body proportions were therefore normal in all patients except for one (case 25), who had a disproportionately large trunk (function score +2·10).

Discussion

Congenital adrenal hyperplasia is associated with hyperandrogenaemia during both prenatal and postnatal life. Plasma testosterone and androstenedione concentrations of 22 nmol/l and 216 nmol/l, respectively, (adult reference ranges for men 10–30 and 4·4–10·6 nmol/l, respectively) have been recorded in a female fetus with congenital adrenal hyperplasia of 22 weeks' gestation (unpublished observation).

Treatment aims to suppress the adrenal production of excess androgens, thereby allowing normal growth and development. Measurements of concentrations of adrenal steroids in plasma and saliva, in addition to monitoring growth, are important indices of therapeutic control, and treatment aims to keep these within the normal range.[1]

Patients in group 2 were carefully monitored and treated with adequate doses of glucocorticoids, yet they showed an increase in bone age over chronological age as a result of mild chronic or intermittent hyperandrogenaemia. Similar treatment regimens were used for patients in group 1 who had fused epiphyses at the time of the study. Neither group, however, showed evidence of body disproportion as a result of excessive truncal growth. This was observed in only one girl with untreated late onset congenital adrenal hyperplasia in whom skeletal maturation was extremely advanced; plasma testosterone and androstenedione concentrations were 18 and 70 nmol/l, respectively.

The results of this study suggest that body proportions are usually normal in congenital adrenal hyperplasia despite chronic or intermittent hyperandrogenaemia, except perhaps where severe hyperandrogenaemia has been present in the postnatal period for some considerable time. In keeping with the results of other studies[2–5] [14] [15] final height was below average in patients in group 1 who had completed their growth. Three of the 11 patients were above average height, while the remainder showed varying degrees of shortness. In seven of these patients (not including case 6), height outcome could be judged in comparison with parental heights; five achieved final heights less than the mid parental height and in two cases this was greater than −2SD below the latter.

Height in those still growing (group 2) was suboptimal, particularly when height SD scores were related to bone age. Loss of height was apparently less in boys than in girls (height SD score for chronological age 0·73 (1·28) and −1·36 (0·97), respectively), but boys had a disproportionate advance in bone age ((bone age−chronological age); for boys 2·71 (2·27), and girls 0·80 (0·98)). This height advantage disappeared when height SD score was expressed for bone age (fig 1). The greater advance in bone age for boys may be the result of a number of factors. The diagnosis is generally established later in boys than in girls, by which time bone age is already advanced. The clinical signs of mild hyperandrogenaemia are likely to be less acceptable in girls.

Previous studies of growth in congenital adrenal hyperplasia have often attributed poor outcome to inadvertent overtreatment with steroids, particularly during infancy when growth retardation may not be followed by catch up growth after dose reduction.[4 5] High dose regimens based on the results of early studies,[16] the use of insensitive measurements of control,[1 10] and excessive steroid treatment at the time of diagnosis and during intercurrent illness[5] are all factors contributing to suppression of growth. The resulting loss in height has generally been associated with a delay in skeletal maturation.[15] Patients in group 2 in this study were treated with lower doses of steroid in general, and more sensitive measurements of control were used for monitoring treatment. Consequently bone age was usually in advance of chronological age and yet the outcome for height was still unsatisfactory in some patients.

Growth is extremely sensitive to exogenous steroids[6 17] and even a small amount of steroid given in excess of physiological requirements may be detrimental.[18] Glucocorticoids can affect the spontaneous secretion of growth hormone[19] and its response to provocative stimulation,[20] but steroid induced inhibition of growth is probably mediated through a more direct action on epiphyseal cartilage metabolism.[6] The results of this study suggest that doses of glucocorticoid that permit a mild advance in skeletal maturation may also be sufficient to restrict growth.

Perhaps some loss of height in patients with congenital adrenal hyperplasia may be inevitable with the treatment regimens currently used. Nevertheless, the potential loss of height can be minimised by ensuring that only the smallest dose of glucocorticoid necessary is used, that mineralocorticoid treatment is given to patients with raised plasma renin activity, and that sensitive biochemical measures of therapeutic control are used to supplement the standard criteria of clinical control.

References

[1] Hughes IA. Management of congenital adrenal hyperplasia. *Arch Dis Child* 1988;**63**:1399–404.

[2] Bergstrand CG. Growth in congenital adrenal hyperplasia. *Acta Paediatr Scand* 1966;**55**:463–72.

[3] Brook CGD, Zachmann M, Prader A, Murset G. Experience with long-term therapy in congenital adrenal hyperplasia. *J Pediatr* 1974;**85**:12–9.

[4] Dimartino-Nardi J, Stoner E, O'Connell A, New MI. The effect of treatment on final height in classical congenital adrenal hyperplasia. *Acta Endocrinol* 1986;**279**(suppl):305–13.

[5] Rappaport R, Cornu G, Royer P. Statural growth in congenital adrenal hyperplasia treated with hydrocortisone. *J Pediatr* 1968;**73**:760–6.

[6] Hughes IA. Steroids and growth. *Br Med J* 1987;**295**:683–4.

[7] Tanner JM, Whitehouse RH, Hughes PCR, Carter BS. Relative importance of growth hormone and sex steroids for the growth at puberty of trunk length, limb length, and muscle width in growth hormone deficient children. *J Pediatr* 1976;**39**:1000–8.

[8] Marshall WA. *Human growth and its disorders*. London: Academic Press, 1977.

[9] Martinez L, Preece MA, Grant DB. Body proportions in precocious puberty. *Acta Paediatr Scand* 1984;**73**:185–8.

[10] Young MC, Robinson JA, Read GF, Riad-Fahmy D, Hughes IA. 17OH-progesterone rhythms in congenital adrenal hyperplasia. *Arch Dis Child* 1988;**63**:617–23.

[11] Smith DW. Growth and its disorders. In: Schaffer JA, Markowitz M, eds. *Major problems in clinical paediatrics*. Vol 15. London: W B Saunders, 1977.

[12] Tanner JM, Whitehouse RH. *Standards for sitting height and sub-ischial leg-length from birth to maturity: British children 1978*. Hertford: Castlemead Publications, 1979.

[13] Tanner JM, Whitehouse RH, Marshall WA, Healy MJR, Goldstein H. *Assessment of skeletal maturity and prediction of adult height (TW2 method)*. London: Academic Press, 1975.

[14] Clayton GW. Patterns of growth from birth to maturity in infants and children with congenital adrenal hyperplasia. *Acta Endocrinol* 1986;**279**(suppl):295–304.

[15] Bailey CC, Komrower GM. Growth and skeletal maturation in congenital adrenal hyperplasia. Review of 20 cases. *Arch Dis Child* 1974;**49**:4–7.

[16] Grumbach MM, Wilkins L. The pathogenesis and treatment of virilizing adrenal hyperplasia. *Pediatrics* 1956;**17**:418–27.

[17] Moell C, Aronson AS, Selvik G. Growth in rabbits during alternate day cortisone injections: near normal growth on days without cortisone. *Acta Paediatr Scand* 1988;**77**:693–8.

[18] Sobel EH, Hahm SYE. Compensatory growth after HLA-typing revelation of incorrect diagnosis of 21-hydroxylase deficiency. *Acta Endocrinol* 1986;**279**(suppl):290–3.

[19] Bierich JR. Serum growth hormone levels in provocative tests and during nocturnal spontaneous secretion: a comparative study. *Acta Paediatr Scand* 1987;**337**(suppl):48–59.

[20] Stempfel RS, Sheikholislam BM, Lebovitz HE, Allen E, Franks RC. Pituitary growth hormone suppression with low dosage, long active corticoid administration. *J Pediatr* 1968;**75**:767–73.

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Identification of factors affecting infant growth in developing countries

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SUMMARY The anthropometric progress of seven infants was followed throughout their first year of life. Weight, length, mid upper arm circumference, triceps and subscapular skinfold thicknesses were measured on a mean (SD) of 30 (6) occasions with weight alone being measured on a further 6 (2) occasions. The effects of infection and energy intake were identified and illustrated using both standard deviation (SD) score graphs for individual subjects, and more traditionally, regression analysis for the group. Diarrhoea and vomiting, pneumonia, and diarrhoea alone each resulted in significant reductions in growth velocity of 30 g/day. Multi-measurement SD score graphs showed the effects of all illnesses, and permitted simultaneous comparison of anthropometric measurements.

The effect of acute infection on growth has been widely studied, predominantly in third world countries. In Mexico[1] and Guatemala[2] the infective causes of weight loss were diarrhoea, dysentery, and bronchopneumonia. In rural Gambia they were gastroenteritis and malaria,[3 4] and in Uganda they were gastroenteritis and measles.[4] A recent study from urban Gambia again identified diarrhoea and also lower respiratory tract infection.[5]

Such studies have traditionally relied upon mean weight deficit calculated by regression analysis to quantify the effects of infection, showing reductions in weight gain of as much as 746 g/month[3] or 22 g/day for the various infections.[5]

An alternative approach is to express weight, and any other available anthropometric measurements, as standard deviation (SD) scores adjusted for age. The graphical presentation of such information has, however, always been limited by an inability to provide a comprehensive anthropometric picture of an individual subject without recourse to five or six separate centile charts.

There is also the question of the appropriateness of the standards used. In adopting the National Center for Health Statistics (NCHS) growth curves[6] as their international standard, the World Health Organisation (WHO) defined their standards for body weight, length, and head circumference.[7] The values that they chose for mid upper arm circumference were based on the data of Wolanski.[8] There were no values adopted for skinfold thickness. In the United Kingdom the most accessible skinfold values are those of Tanner and Whitehouse.[9] The data for all these standards were collected between 15 and (in the case of the NCHS values for infants) 59 years ago. These standards are taken from different populations and their use to provide a composite set of multiple anthropometric measurements for an individual subject is of doubtful value.

A set of centiles that allows a comparison of several measurements is that derived from the data of an infant growth study in Cambridge, United Kingdom.[10–12] The centiles cover weight, length, mid upper arm and head circumference, and triceps and subscapular skinfold thicknesses. They are constructed using the LMS method, which gives smooth centile curves while adjusting for skewness thus permitting skewed data (such as weight or skinfold thickness) to be presented in SD form.[13 14] The method also allows the conversion of SD scores directly into centile values using normal distribution tables. An SD (or Z) score of, for example, an infant's weight at a given age, expresses weight relative to the population mean in the form of a normally distributed variable that has a mean of zero and an SD of one. An SD score can be positive or negative, depending on whether the weight is above or below the mean, and an infant growing along the 50th centile will, on an SD score graph, appear on the horizontal line corresponding to zero. The range of values can be set as required, but the range of normal is conventionally from −2 SD to +2 SD. The use of SD scores is in line with the WHO recommendations[7 15] and using these centiles it is possible to construct, on one graph, a set of SD scores for multiple measurements, which permit all a child's anthropometric measurements and the factors affecting them to be viewed at once.

In the present study we prospectively followed seven infants through their first year of life to identify those factors affecting their growth such as frequent acute infection—and to assess SD score graphs of multiple measurements as a means of presenting a comprehensive anthropometric picture of individual infants.

Subjects and methods

The study took place in the village of Keneba, which is in the Kiang West district of The Gambia, West Africa. It is a rural subsistence farming community and has been the site of a nutritional field station for 15 years. It has a population of 1250 and the community has previously been described in detail.[16 17]

Seven sequential births from the village were recruited to a study[18] of which this formed one part. The study lasted for the first year of the infants' lives.

Measurements were made of body weight, length, mid upper arm circumference, and triceps and subscapular skinfold thickness. These were measured every 14 days when the infants were well and up to six times in the 21 days after the onset of an episode of acute illness. All the measurement were made by one person (MPE). The values were converted into SD scores using the methods described by Cole,[13] and were then plotted, with all of an individual infants' five sets of values on one graph.

To establish a coefficient of variation for each measurement, repeated short term measurements were made on a group of 10 children. Coefficients of variation were low, being <0·1% for weight and head circumference, 2·8% for mid upper arm circumference, and 6·6% for skinfold thicknesses.

Illnesses were recorded and treated at the daily, open access, medical clinic held in the village. Diagnoses were made by either of the resident clinicians according to predetermined criteria.[18] The infants did not attend any other medical service. The illnesses fell into 11 diagnostic groups and for the purposes of the regression analysis each was represented by a two letter code, for instance pneumonia was coded as RP and diarrhoea as DU.

The effect of infection on weight gain was calculated by regression analysis using the Genstat 5 statistical language. Weight gain was calculated, in g/day, as the difference between successive weights divided by the time interval in days. Individual weights were coded in two ways. Absence of illness was coded as 'well' and a weight measured during an episode of illness was coded by a single diagnosis with time from onset. Thus weights measured on the third, seventh, 10th, and 13th days of an episode of pneumonia were coded as RP03, RP07, RP10, and RP13. Well measurements were coded as WE00. Using five days as the duration of an illness, binary independent variables were constructed for each illness category to indicate whether or not they were present during a time interval. Measurements were also coded by stage of illness as acutely unwell (defined clinically), convalescent (14 days after being acutely unwell), and well.

The study was approved by the joint Medical Research Council and Gambian government ethics committee.

Table *Number of episodes of illness for each infant. Total number of days that the infant was ill is shown in parentheses*

Illness	*Case No*						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Upper respiratory tract infection	6 (31)	1 (3)	6 (29)	1 (6)	4 (24)	2 (11)	3 (24)
Tonsillitis	1 (5)	0	1 (6)	0	2 (7)	0	0
Otitis media	2 (11)	8 (50)	2 (8)	0	2 (11)	6 (35)	1 (5)
Pneumonia	2 (9)	0	0	0	2 (9)	0	1 (3)
Diarrhoea alone	3 (17)	2 (18)	7 (39)	1 (7)	0	2 (17)	1 (12)
Diarrhoea and vomiting	0	1 (4)	1 (11)	1 (4)	1 (5)	1 (16)	1 (5)
Vomiting alone	0	0	0	0	0	0	1 (6)
Malaria	1 (3)	0	1 (3)	0	0	0	0
Abscess	1 (6)	0	0	0	1 (7)	0	0
Urinary tract infection	0	0	0	0	1 (6)	0	0
Fever	2 (9)	0	3 (17)	1 (7)	4 (17)	1 (5)	0
All illnesses	18 (91)	12 (75)	21 (113)	4 (24)	17 (86)	12 (84)	8 (55)

Results

The illnesses from which the infants suffered were divided into 11 diagnostic groups (table). These patterns of morbidity, which are extreme, produced a mean (SD) period of acute illness of 75 (29) days/infant. The mean duration of an episode of illness was 5·7 (2·4) days.

The infants had all five anthropometric measurements made on a mean of 30 (6) occasions, with weight alone being measured on a further 6 (2) occasions. The mean interval between weights used for the calculation of weight gain was 10 (7) days.

The effects of infection calculated by regression analysis were significant for three illnesses: diarrhoea and vomiting, pneumonia, and diarrhoea. Falls in weight gain were respectively: 33 g/day ($p<0{\cdot}01$), 32 g/day ($p<0{\cdot}01$), and 34 g/day ($p<0{\cdot}05$). Despite the significance of the difference from when they were well, they were not significantly different from one another. The growth rate increments for convalescence and 'well', expressed as positive increments compared with when ill, were 20 g/day ($p<0{\cdot}001$) and 16 g/day ($p<0{\cdot}01$), respectively. Again, despite their significant differences from when ill, they were not significantly different from each other.

The SD score graphs for the individual infants are shown in figs 1–7. The effect of illness on growth is clearly seen in the graphs, as with case 1 at 30 weeks or case 6 at 39 weeks. The effects of infection are reflected in all measurements, even length. With

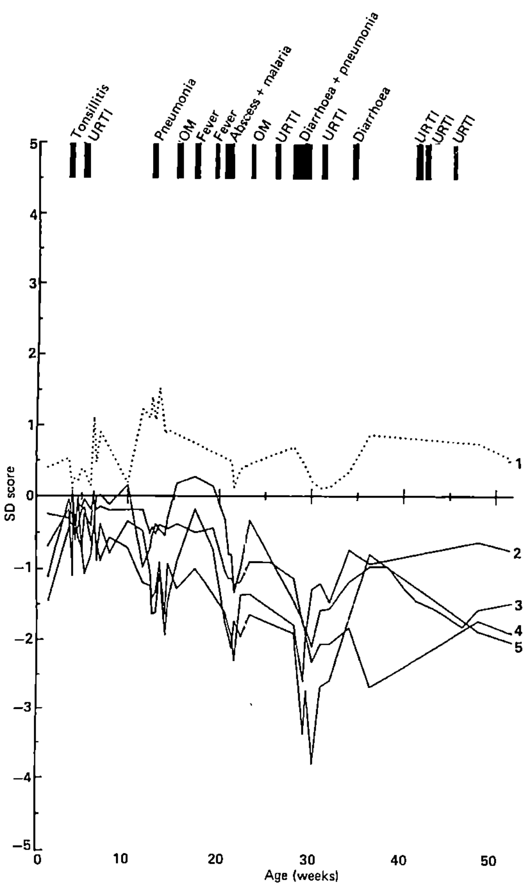

Fig 1 *SD scores for case 1. OM=otitis media, URTI=upper respiratory tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

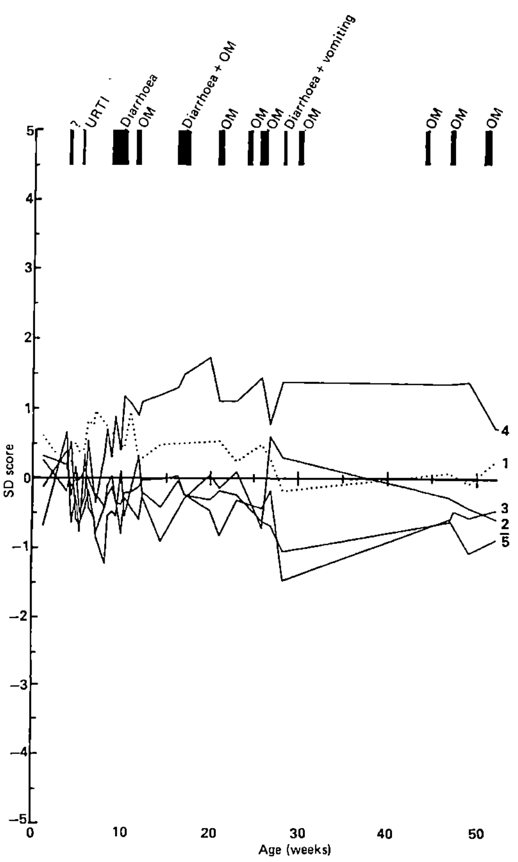

Fig 2 *SD scores for case 2. OM=otitis media, URTI=upper respiratory tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

the exception of length and mid upper arm circumference all the measurements are significantly correlated with each other ($p<0 \cdot 001$). It is noticeable that the illnesses producing the largest deviations are those identified by regression analysis as causing significant falls in weight gain. With the exception of case 5, growth in length is maintained while the other measurements, particularly weight and mid upper arm circumference, fall consistently, showing that the infants are wasting. Case 5 shows a degree of stunting. With the exception of cases 2 and 3, the graphs also show that infection produces modulations on an underlying trend. There is an initial variable rise (pronounced in cases 5 and 7) with a universal subsequent fall with most of the values finishing up at −1·5 to −2 SD.

Discussion

The results of this study confirm the growth faltering effects of gastroenteritic and lower respiratory tract disease in infants in third world countries. This is shown qualitatively for individual infants by the multiple measurement standard deviation score graphs, and quantitatively for all infants by the regression analysis.

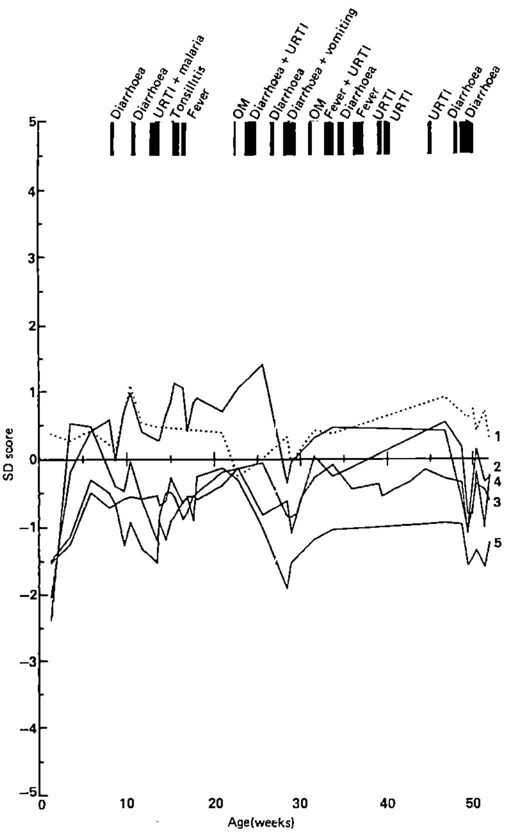

Fig 3 *SD scores for case 3. OM=otitis media, URTI=upper respiratory tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

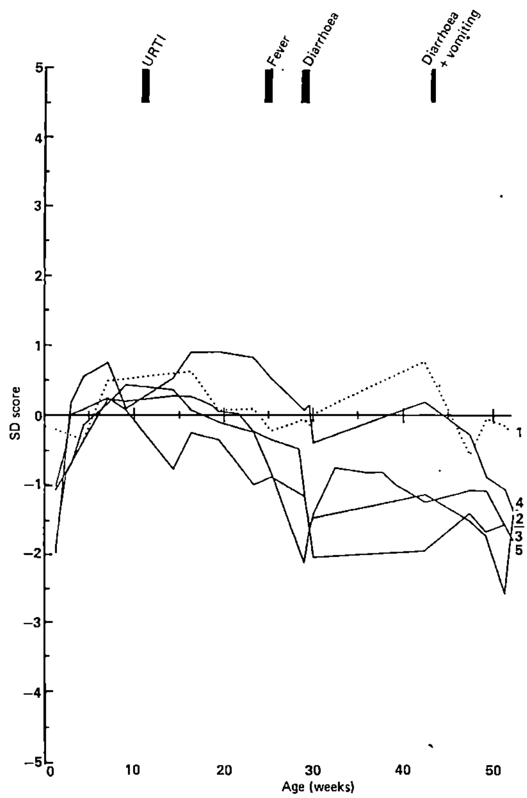

Fig 4 *SD scores for case 4. URTI=upper respiratory tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

The multiple measurement SD score graphs allow the whole anthropometric progress of an infant to be viewed at once. The significant effects of gastroenteritis and pneumonia are easily seen on the graphs, as are the growth faltering effects of other episodes of illness.

It is important to understand the justification for using the Cambridge growth curves in a West African population. The Cambridge data set has all its measurements drawn from the same infants, giving it a cohesion not present in other data sets and allowing 'across measurement' comparisons to be soundly based. The LMS method provides (uniquely) SD scores for skewed variables like

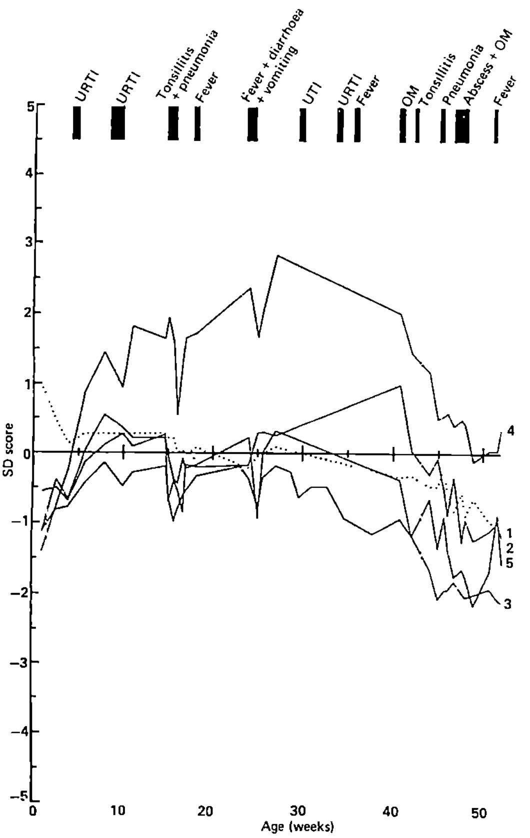

Fig 5 *SD scores for case 5. OM=otitis media, URTI=upper respiratory tract infection, UTI=urinary tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

weight and skinfold thickness, and it is this that allows the construction of the SD score graphs. Furthermore, the growth curves are based upon infants who were fed in the manner currently recommended by the DHSS.[19] This permits prolonged breast feeding and more closely resembles the feeding patterns of the Keneba infants. Given that infant feeding patterns affect growth it is sensible to use growth curves that are as appropriate as possible in this respect.[11]

In all the infants the graphs identify not only the effects of illness but also a steady fall in the SD score for weight from about 15 weeks of age. As all the infants except case 5 maintained their growth in length, this represents wasting. With his steady fall off in both weight and length, case 5 shows evidence of stunting, a feature of growth that is, in Keneba, more normally seen after infancy.

The size of the weight deficit over infancy is calculable. Using the figures for 'convalescence/well' it is possible to calculate the mean weight deficit in the seven infants caused by acute infection, and thus the weight deficit from other causes. The infants were acutely unwell for 20% of the time, convalescent for 34% of the time, and well for 46% of the time. The deficit for acute illness is: 16 g/day×0·2=3·2 g/day. Had the infants never been acutely unwell they would never have been convalescent so this figure of 3·2 g/day has to have subtracted from it the difference between being well and being convalescent: (20–16)×0·34=1·4 g/day. This produces an overall figure of 1·8 g/day weight deficit as a result of infection, which produces a total of almost 700 g over the first year of life.

The mean weight deficit at 12 months, measured from the Cambridge growth curve 50th centile for

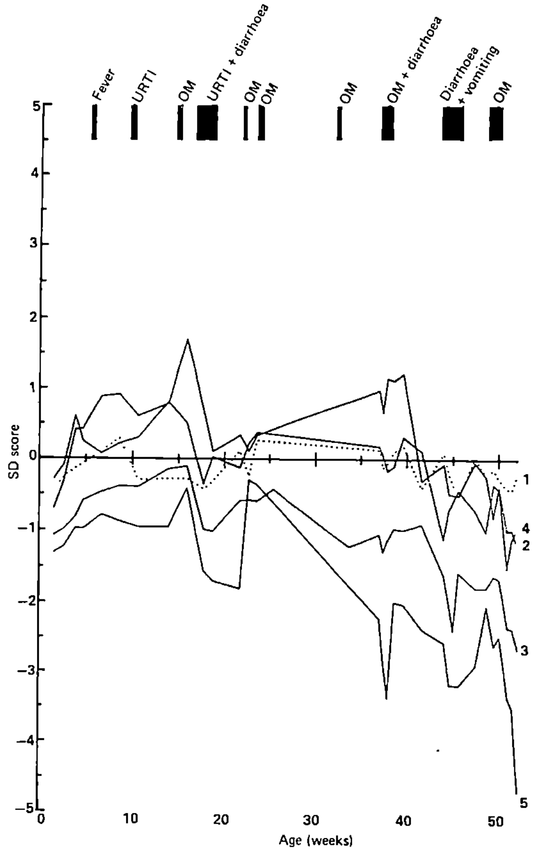

Fig 6 *SD scores for case 6. OM=otitis media, URTI=upper respiratory tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

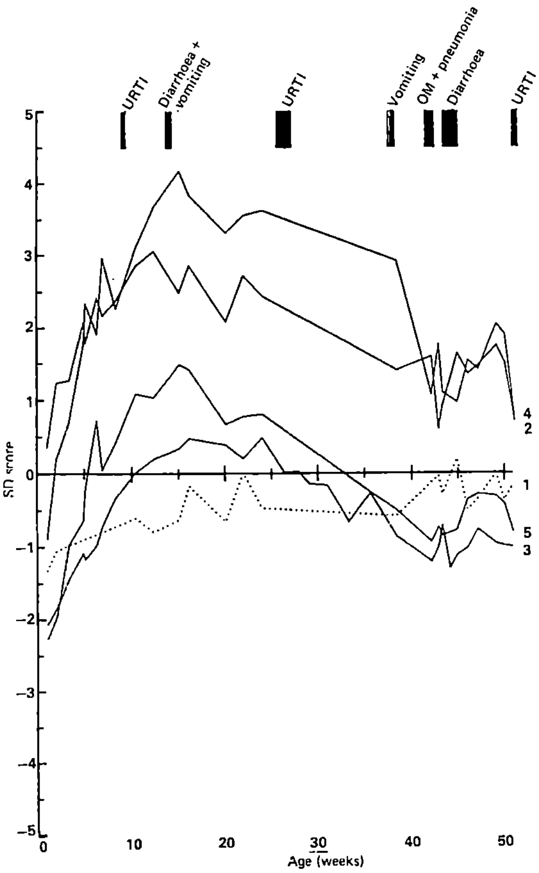

Fig 7 *SD scores for case 7. OM=otitis media, URTI=upper respiratory tract infection; 1=length, 2=subscapular skinfold thickness, 3=weight, 4=triceps skinfold thickness, and 5=mid upper arm circumference.*

weight, was 1200 g. The 700 g deficit calculable as a result of infection represents 58% of this total leaving 42% (500 g) of the weight deficit resulting from other causes. This figure of 500 g corresponds to the slow fall in the SD score of weight seen in the graphs.

A similar picture of weight loss was found by Rowland *et al* working in Bakau, an urban community on The Gambia's Atlantic coast.^{5} Using as their standard the NCHS growth curves^{6} they found an illness related weight deficit of 900 g at 12 months, broadly similar to the 700 g that we found. Their total weight deficit was, however, only a further 300 g, whereas the corresponding Keneba value, having allowed for the 400 g difference between the means of the two standards, is a further 900 g; this is three times the Bakau figure.

When comparing Keneba and Bakau, Tomkins *et al* showed seasonal swings in growth rates in both communities.^{20} These swings were larger in Keneba where seasonal food shortage, as opposed to Bakau's year round availability of food, was thought to account for much of the difference in growth performance between the two communities. Although food intake was not measured in this study, previous work in Keneba has shown infant energy intake to be low and an underlying deficiency in energy intake provides a rational explanation for the steady wasting seen in the SD score graphs.^{21}

The illnesses producing an impact on growth are similar to those identified by previous authors. Diagnostic criteria vary, but the diagnoses of diarrhoea, and diarrhoea and vomiting, in this study can be equated with diarrhoea or gastroenteritis from other studies.$^{1\ 3-5}$ Previous work in Keneba identified diarrhoeal disease as an important cause of weight loss with a fall in weight gain of 25 g/day.^{3} This is similar to the figure of 34 g/day found in this study and shows that the cost in terms of weight gain associated with infant diarrhoea in this rural community has unfortunately not changed over the last 10 years. It is also worth noting that the study of Rowland *et al*^{5} and this study both identified lower respiratory tract infection as an important cause of failure of growth.

SD score graphs provide a powerful method of identifying and highlighting problems with growth resulting from, in this case, the effects of infection and undernutrition. This has not previously been possible because of the lack of an adequate multimeasurement standard. These effects are statistically calculable within the group, but when considering an individual subject the use of SD score graphs permits both the time scale and the accurate progress of an individual subject to be clearly seen. Moreover the curves permit simultaneous comparison across five different anthropometric measurements and the demonstration of the effects of those illnesses that cause growth faltering in an individual subject but do not achieve significance within the group. Although applied here to the acute and chronic problems of infants in the third world, these graphs could equally well be used to record the anthropometric progress of any child suffering from any acute (for example, infective) or chronic (for example, coeliac disease) condition.

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References

[1] Condon-Paoloni D, Cravioto J, Johnston FE, De Licardie ER, Scholl TO. Morbidity and growth of infants and young children in a rural Mexican village. *Am J Public Health* 1977;**67**:651–6.

[2] Mata LJ, Urrutia JJ, Abertazzi C, Pellecer O, Arellano E. Influence of recurrent infections on nutrition and growth of children in Guatemala. *Am J Clin Nutr* 1972:**25**:1267–75.

[3] Rowland MGM, Cole TJ, Whitehead RG. A quantitative study into the role of infection in determining nutritional status in Gambian village children. *Br J Nutr* 1977;**37**:441–50.

[4] Cole TJ, Parkin JM. Infection and its effects on the growth of young children: a comparison of The Gambia and Uganda. *Trans R Soc Trop Med Hyg* 1977;**71**:196–8.

[5] Rowland MGM, Goh Rowland SGJ, Cole TJ. The impact of infection on the growth of children from 0 to 2 years in an urban West African community. *Am J Clin Nutr* 1988;**47**:134–8.

[6] National Center For Health Statistics. *NCHS growth curves for children, birth-18 years.* Washington: US Department of Health Education and Welfare, 1977.

[7] Waterlow JC, Buzina R, Keller W, Lane JM, Nichaman MZ, Tanner JM. The presentation and use of height and weight data for comparing the nutritional status of children under the age of 10 years. *Bull WHO* 1977;**55**:489–98.

[8] Wolanski N. Standards for arm circumference. Quoted in: Jelliffe DB. *The assessment of nutritional status in the community.* Geneva: World Health Organisation, 1966. (WHO Monograph Series No 53.)

[9] Tanner JM, Whitehouse RH. Revised standards for triceps and subscapular skinfolds in British children. *Arch Dis Child* 1975;**50**:142–5.

[10] Whitehead RG, Paul AA. Growth charts and the assessment of infant feeding practices in the western world and in developing countries. *Early Hum Dev* 1984;**9**:187–207.

[11] Whitehead RG, Paul AA, Ahmed EA. Weaning practices in the United Kingdom and variations in anthropometric development. *Acta Paediatr Scand* 1986;**323**(suppl):14–23.

[12] Whitehead RG, Paul AA, Ahmed EA. DHSS present day infant feeding practice and its influence on infant growth. In: Tanner JM, Preece MA, eds. *The physiology of growth.* Proceedings of the society for the study of human biology. Symposium No 29. Cambridge: Cambridge University Press, 1989.

[13] Cole TJ. Fitting smoothed centile curves to reference data. *Journal of the Royal Statistical Society* (*Series A*) 1988;**151:** 385–418.

[14] Cole TJ, Paul AA, Eccles MP, Whitehead RG. The use of a multiple growth standard to highlight the effects of diet and infection on growth. In: Tanner JM, ed. *Auxology '88: perspectives in the science of growth and development.* London: Smith, Gordon, 1989.

[15] World Health Organisation. *Measuring change in nutritional status.* Geneva: World Health Organisation, 1983.

[16] Thompson B. Marriage, childbirth and early childhood in a Gambian village: a socio-medical study. Aberdeen: University of Aberdeen, 1965. 353 pp. (PhD thesis.)

[17] Lamb WH. A prospective study of psychomotor development in rural West African (Gambian) infants. Newcastle: University of Newcastle upon Tyne, 1987. 299 pp. (MD thesis.)

[18] Eccles M. A prospective study of the effects of frequent infection on the energy metabolism of Gambian infants. Newcastle: University of Newcastle upon Tyne, 1988. 235 pp. (MD thesis.)

[19] Report of a Working Party of the Panel on Child Nutrition, Committee on Medical Aspects of Food Policy. *Department of Health and Social Security. Report on health and social subjects 20: present day practice in infant feeding. 1980.* London: HMSO, 1983.

[20] Tomkins AM, Dunn DT, Hayes RJ, Bradley AK. Seasonal variations in the nutritional status of urban Gambian children. *Br J Nutr* 1986;**56**:533–43.

[21] Whitehead RG, Rowland MGM, Hutton MA, Prentice AM, Muller EM, Paul AA. Factors influencing lactation performance in rural Gambian mothers. *Lancet* 1978;**ii**:178–81.

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Growth in atopic eczema: a controlled study by questionnaire

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SUMMARY The parents of 128 children with atopic eczema and 117 healthy control children responded to a questionnaire that included measurement of their own and their children's heights at home after standardised instructions. When cases and controls were compared there was no significant difference in parental height but the children with eczema were significantly shorter than the healthy control group. This difference remained significant when children with associated asthma were excluded from the analysis.

Numerous authors have examined the growth pattern of asthmatic children but,[1–7] to our knowledge, only one study has addressed the question of growth in atopic eczema.[8] This study was not controlled and did not fully exclude the effect of concurrent asthma.

We have used a questionnaire to obtain the heights of children with eczema, matched non-eczematous controls, and the parents of these two groups. The questionnaire was also used to establish whether concurrent asthma was present in order to identify a group of non-asthmatic eczematous children for separate analysis.

Patients and methods

The parents of all 148 children who had been seen in one consultant dermatologist's clinic at the Hospital for Sick Children, Great Ormond Street, with a diagnosis of atopic eczema between 1982 and 1985 were sent questionnaires. Each family was sent an envelope that contained two smaller sealed envelopes enclosing questionnaires for the individual child and for a control to be selected by the parents. A letter instructed the parents to give the control questionnaire to a friend with a child of approximately the same age as their own child but who had never had eczema. They were instructed to do this before opening the envelopes containing their own or the control child's questionnaire.

The questionnaire included questions about paternal employment and the presence or absence of asthma. The parents were asked to indicate the date of birth and heights of themselves and their child. Instructions as to the measurement of height were as follows: 'It is *very important* that the heights *are very accurate.* Please take shoes and socks off. Stand straight with heels and back against a wall. Someone else should then put a large firm book on your head as flat as possible and draw a line on the wall where the book touches it. Measure the distance from the floor to the line on the wall as carefully as you can with a tape measure. You can use feet and inches or metres and centimetres. Please do not include stepmothers or stepfathers'.

Where no response was received to a questionnaire it was followed by a second letter.

Height standard deviation (SD) scores were calculated using the formula

$$\text{SD score} = \frac{x - \bar{x}}{Sx}$$

where x is the height measured, $\bar{x}$ the mean height for the age of the individual concerned and Sx is the standard deviation for height at a given age.[9 10]

Results

RESPONSE

A total of 245 replies were received: 128 cases and 117 controls (83% of the total 296 sent). Not every reply was complete: of the replies from parents of children with eczema, 115 indicated the child's height, 125 the mother's height, and 124 the father's height; of the replies from the parents of controls 110 indicated the child's height, 110 the mother's

Table *Comparison of children with eczema and controls with respect to parental and children's SD scores for height: (a) all children, (b) children without a history of asthma, antiasthmatic medication, or oral steroids, and (c) children over 5 years without a history of asthma, antiasthmatic medication, or oral steroids*

	Children with eczema		*Controls*		*Difference by t test (p value)*
	No	*Mean SD score (SE)*	*No*	*Mean SD score (SE)*	
(a) All children:					
Mothers	125	0·2505 (0·102)	110	0·2777 (0·106)	NS
Fathers	124	0·1622 (0·094)	111	0·2025 (0·115)	NS
Children	115	−0·4505 (0·119)	110	0·0595 (0·097)	<0·0005
(b) No history of asthma, antiasthmatic medication, or oral steroids:					
Mothers	55	0·2429 (0·149)	108	0·2877 (0·108)	NS
Fathers	55	0·2118 (0·138)	107	0·2059 (0·116)	NS
Children	52	−0·4465 (0·177)	107	0·0518 (0·099)	<0·01
(c) Aged over 5 with no history of asthma, antiasthmatic medication, or oral steroids:					
Mothers	25	0·4416 (0·221)	71	0·2204 (0·132)	NS
Fathers	25	0·1408 (0·226)	70	0·1546 (0·130)	NS
Children	22	−0·7232 (0·346)	70	0·1416 (0·123)	<0·005

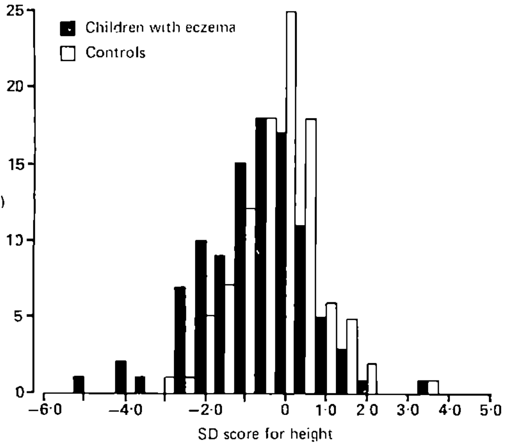

Figure *Distribution of SD scores for height for children with eczema and controls.*

height, and 111 the father's height. The mean age of the children with eczema where there was a response was 6·9 years (range 1·2–16·2 years) and of the controls 7·0 years (range 1·1–16·5 years), there being no significant difference between the two. Fifty percent of children with eczema and 52% of controls were boys. There was no significant difference in social class as judged by paternal employment between the two groups (χ_3^2=1·43, p>0·5).

HEIGHTS

There was no significant difference between the SD score of the parents of either group. The mean SD score of children with eczema was significantly less than that of controls, which was itself close to that of the population mean (table (a) and figure). Though the difference was not significant, the parents of cases were shorter than the parents of controls (table (a)). Analysis of covariance was used to correct for this difference and the regression intercept coefficients showed a significant difference between children with eczema and controls allowing for the difference in parental height (p<0·0005, *t* test).

Fifty seven children with eczema answered negatively to questions relating to the presence of asthma and to the use of antiasthmatic medication or oral steroids at any stage in their lives. Comparison of the SD scores of these families with those of the control group who also responded negatively to these questions again produced no significant differences between parents but significant differences between the children (table (b)). When the age of this subgroup was considered, the children with eczema (mean age 5·7 years) were found to be significantly younger than controls (mean age 7·1 years) (p<0·05, *t* test). Analysis of covariance was again used confirming that the difference in SD scores between cases and controls remained significant (p<0·01) after correction for differences in age and in parental height.

As the onset of asthma is later than that of atopic eczema and an eczematous preschool age child without respiratory symptoms might subsequently develop asthma, the same comparisons illustrated in the table (b) were made excluding children under the age of 5 years. Again a significant difference ($p<0{\cdot}005$, *t* test) in SD scores between children with eczema and controls was found that could not be explained on the basis of an age or parental height difference (table (c)).

Discussion

Only one study to date has assessed the growth of eczematous children.[8] This detailed uncontrolled cross sectional study found that 10% of 89 patients had heights below the third centile and that, of the 69 patients between 2 and 9 years of age where correction for midparental height could be performed, 22% fell below the 10th centile and only 9% had a corrected height above the 90th centile. The children also showed delayed skeletal maturity, large head circumferences, a disproportionately shorter sitting height compared with subischial leg length, and a normal skinfold thickness. Increasing disease extent, steroid potency, and asthma severity were associated with decreasing height centile but none of these three factors could be excluded.

Our own study was also cross sectional and the measurement of height was performed by parents at home in a clearly less accurate fashion. We did not assess other anthropometric data (sitting height, skinfold thickness, etc). Our numbers were greater, however, and our study included a well matched control group who followed the same instructions as to measurement as the eczematous group. Hence, although our heights are individually less reliable as absolute measurements, the significant difference found between eczematous and non-eczematous children remains valid. Furthermore, using questionnaire answers, we were able to exclude the effect of concurrent asthma, a disease that is well known to be associated with an abnormal growth pattern.[1-3 6] Like the study reported by Kristmundsdottir and David,[8] our patients came from a tertiary referral centre and were therefore likely to be more severely affected than the eczematous population as a whole.

Our findings indicate that children with eczema, who do not have asthma, are shorter than genetically expected from assessment of parental heights. While most of our eczematous group were not very short, 12 were more than 2 SDs below the mean and four were more than 3 SDs below the mean. Of these 12 very short children, six had been diagnosed as asthmatic.

The growth pattern of asthmatic children has been shown to be that of growth delay with a delayed pubertal growth spurt and a normal adult height.[3 7 11 12] The cross sectional nature of our study prevents us establishing whether eczematous children follow a similar pattern. Ferguson *et al*, comparing asthmatics with children with allergic rhinitis and finding no difference, have suggested an underlying abnormality of growth pattern related to the atopic state rather than to asthma itself,[13] and our findings are consistent with this hypothesis.

While growth delay may be the most likely cause of the height difference we have observed, alternative explanations for this include: (i) an effect of topical corticosteroids, (ii) nutritional factors, and (iii) an effect of sleep disturbance. It is extremely difficult to quantify lifetime topical corticosteroid use and difficult to separate its influence on growth from the influence of the eczema itself, as children with more severe eczema tend to have had greater topical corticosteroid exposure. Nutritional factors might play a part as gastrointestinal function is known to be abnormal in a proportion of eczematous children.[14 15] Growth failure due to transcutaneous protein loss has been reported in eczema,[16] and failure to thrive has been shown to result from inappropriate exclusion diets,[17] and eczema is frequently treated by dietary modification. The normal weight and skinfold thickness observed by Kristmundsdottir and David,[8] however, do not suggest a nutritional aetiology. Sleep disturbance due to pruritis is a well recognised feature of atopic eczema and might adversely affect the secretion of growth hormone and gonadotrophins which, in the normal circadian rhythm, is principally nocturnal.

Controlled longitudinal studies of non-asthmatic eczematous children are needed to establish whether the difference we have observed represent an effect of the disease or its treatment, or simply a physiological growth pattern associated with the atopic state.

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References

1. Falliers CJ, Szentivanyi J, McBride M, Bukantz S. Growth rate of children with intractable asthma. *J Allergy* 1961;**32**:420–34.
2. Spock A. Growth patterns in 200 children with bronchial asthma. *Ann Allergy* 1965;**23**:608–15.
3. Snyder RJ, Collipp PJ, Greene JS. Growth and ultimate height of children with asthma. *Clin Pediatr* 1967;**6**:389–92.
4. Sanders SS, Norman AP. Growth hormone secretion in growth-retarded asthmatic children. *Br Med J* 1969;**iii**:25–6.
5. Morris HG. Growth and skeletal maturation in asthmatic children: effect of corticosteroid treatment. *Pediatr Res* 1975;**9**: 579–83.

[6] Murray AB, Fraser B, Hardwick SF, Pirie G. Chronic asthma and growth failure in children. *Lancet* 1976;**ii**:197–8.

[7] Hauspie R, Susanne C, Alexander F. Maturational delay and temporal growth retardation in asthmatic boys. *J Allergy Clin Immunol* 1977;**59**:200–6.

[8] Kristmundsdottir F, David TJ. Growth impairment in children with atopic eczema. *J R Soc Med* 1987;**80**:9–12.

[9] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. Part I. *Arch Dis Child* 1966;**41**: 454–71.

[10] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. Part II. *Arch Dis Child* 1966;**41**:613–35.

[11] Balfour-Lynn I. Growth and childhood asthma. *Arch Dis Child* 1986;**61**:1049–55.

[12] Shohat M, Shohat T, Kedem R, Mimouni M, Danon YL. Childhood asthma and growth outcome. *Arch Dis Child* 1987;**62**:63–5.

[13] Ferguson AC, Murray AB, Tze W-J. Short stature and delayed skeletal maturation in children with allergic disease. *J Allergy Clin Immunol* 1982;**69**:461–6.

[14] Pike MG, Heddle RJ, Boulton P, Turner MW, Atherton DJ. Increased intestinal permeability in atopic eczema. *J Invest Dermatol* 1986;**86**:101–4.

[15] Jenkins HR, Walker-Smith JA, Atherton DJ. Protein-losing enteropathy in atopic dermatitis. *Pediatr Dermatol* 1986;**3**: 125–9.

[16] Abrahamov A, Schifmann R, Tal Y, Freir S. Growth failure due to protein loss in dermatitis. *Eur J Pediatr* 1986;**145**:223–6.

[17] Tarnow-Mordi WO, Moss C, Ross K. Failure to thrive owing to inappropriate diet free of gluten and cows' milk. *Br Med J* 1984;**289**:1113–4.

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Early diet in preterm babies and developmental status in infancy

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SUMMARY Few data from randomised prospective studies address whether early diet influences later neurodevelopment in man. As part of a larger multicentre trial, 502 low birthweight infants were assigned randomly, for a median of 30 days, to receive a preterm formula or unfortified donor breast milk as sole diets or as supplements to their mothers' expressed milk. Surviving infants were assessed at nine months after their expected date of delivery without knowledge of their feeding regimen. The mean developmental quotient was 0·25 standard deviations lower in those fed donor breast milk rather than preterm formula. In infants fed their mother's expressed milk, however, the disadvantage of receiving banked milk compared with preterm formula as a supplement, was greater when the supplement was over half the total intake, and approached five points, representing 0·5 standard deviations for developmental quotient. Infants fed donor breast milk were at particular disadvantage following fetal growth retardation, with developmental quotients 5·3 points lower.

We suggest that the diet used for low birthweight babies over a brief, but perhaps critical, postnatal period has developmental consequences that persist into infancy; infants who are small for gestational age are especially vulnerable to suboptimal postnatal nutrition.

Whether early diet influences later development is a key question in infant nutrition that has stimulated numerous investigations in animals and man. Most animal studies have been in rats, whose young are very immature at birth. In such experiments both prenatal and early postnatal malnutrition may have significant neurological consequences including a serious loss of brain cells found at necropsy,[1 2] a brain-weight deficit that usually remains after nutritional rehabilitation,[3–5] and impaired performance in learning tasks and visual discrimination tests.[6]

In human infants who have died of severe malnutrition, the total number of brains cells has been found to be reduced by 15–20%, and by 60% in those born weighing under 2000 g,[7] which suggests that all low birthweight infants (whether or not they are small for gestational age) are especially vulnerable to poor postnatal nutrition. Human studies on early diet and later neurodevelopment, however, are difficult to interpret. Much work in humans concerns the consequences of malnutrition in developing countries, where poor diet is associated with medical and social problems that confound any analysis. Thus some workers report behavioural or intellectual benefits from dietary supplementaion following malnutrition in infancy,[8 9] whereas others suggest that stimulation was essential for these benefits.[10] Evidence indicating that early nutrition may have lasting neurodevelopmental effects has, however, come from many other sources. These include studies on malnutrition associated with disease (for instance, infantile hypertrophic pyloric stenosis, which has been associated with later deficits in attention and memory[11]) and with the effects of specific nutrient deficiencies (for example, iron[12]).

Nevertheless it has been difficult to conduct controlled randomised trials to test the hypothesis that early diet is critical for later neurodevelopment in humans. We considered that the preterm infant, born during a phase of rapid brain growth, would be an important model for such a study; currently used diets differ greatly in composition and randomised dietary assignment is practical. Furthermore a conclusive outcome trial would have important implications for clinical management.

We have therefore conducted a prospective, randomised five centre trial of the effect of diet on long term neurodevelopment in infants weighing under 1850 g at birth. The cohort will be followed into adult life; the first formal follow up was 18 months after their expected date of delivery, but in three East Anglian centres we also examined surviving infants at nine months after their expected date of delivery. Our findings at nine months are reported here.

Patients and methods

All infants weighing less than 1850 g admitted to the neonatal units in Cambridge, Ipswich, or King's Lynn over the three year period 1982–4 were entered into this study. Babies were excluded only if they had a major congenital abnormality known to impair growth or development (for example, trisomy), or if they died before randomisation (within the first 48 hours). Approval was obtained for the study from the local ethics committee in each of the trial centres. An important aspect of this study is that after detailed explanation of the study to the guardian(s), consent for the infant to take part was never withheld, so that there was no selection bias in the cohort.

Each mother was asked whether or not she wished to provide expressed breast milk for her infant. If a mother chose not to provide her milk, the infant was randomly allocated either banked donor breast milk or preterm formula as the sole diet (trial 1). Infants whose mothers elected to provide breast milk were randomly allocated (trial 2) either banked donor breast milk or preterm formula as a supplement to be used when mothers were unable to provide sufficient milk to meet their infants' enteral feed volume requirements. The median intake of maternal milk in this 'supplement trial' was 53% of the infants' feed volume during the study. Randomisation, by permuted blocks of variable length, was stratified by centre and birth weight; infants whose birth weight was below 1200 g were randomised separately. Full details of the randomisation, feeding regimens, and preterm formula composition have been published elsewhere,[13] but briefly, the preterm formula contained 2 g protein, 0·335 MJ (80 kcal), 35 mg phosphorus, 70 mg calcium, and 45 mg sodium 100 ml. Before the start of the study in 1982 all infants in the three centres were fed on human milk (banked, or mothers' own, or a combination).

Extensive data were collected on obstetric, fetal, and neonatal factors. The Registrar General's classification was used to code social class[14]; birth rank is the infant's birth order in the living children of the family, infants from multiple births being assigned equal rank.

The assigned diet was discontinued at the time of discharge from the neonatal unit or when a weight of 2000 g had been attained. After discharge from the neonatal unit mothers fed their infants as they and their local advisers chose.

Children were invited for follow up examination nine months after their expected date of delivery. The median age at follow up was 40·4 weeks (lower quartile 39·6, upper quartile 41·7). Full history and physical examination were undertaken by RM in Cambridge and King's Lynn, and by MB in Ipswich.

Knobloch *et al's* developmental screening inventory was given to each child to assess five fields of behaviour: adaptive, gross motor, fine motor, language, and personal-social.[15] For each field a quotient adjusting for prematurity was calculated as follows: observed maturational age divided by attained age from expected date of delivery multiplied by 100; an overall developmental quotient was calculated as the mean of the five scores for each subject. It should be emphasised that the assessment at this and subsequent periods was done with the assessor having no access to data on previous dietary assignment.

In addition to developmental testing, the infants were assessed neurologically by the same examiner with the method described by Amiel-Tison and Grenier.[16] Infants were categorised as neurologically normal, equivocal, or impaired. The tests lay particular emphasis on abnormalities in tone in the diagnosis of neurological impairment. Although 18 month developmental data are not reported here, we have included the assessment of neurological impairment that was made at 18 months with the same tests.

Developmental scores for neurologically impaired infants can be a poor measure of their intellectual development, as many test items require manipulative skills appropriate for age. Results have therefore been analysed separately for infants diagnosed as being impaired at nine months. Statistical analysis was by Student's t test; results are also shown as 95% confidence intervals. Tests for interaction were performed to determine whether the dietary effect on development differed significantly between contrasting subgroups (for example, boys compared with girls, or small compared with appropriate size for gestational age). The significance of this interaction was assessed by comparing the differences in dietary effect between two subgroups, again by Student's t test.

Results

Altogether 502 infants were enrolled in this study. The mothers of 343 (68%) chose to provide their breast milk, those of 159 (32%) elected not to do so. Table 1 shows the mortality before nine months after the expected date of delivery, and the demographic and clinical details of surviving infants in each group who were successfully followed up at this age. Fifty nine surviving children were not seen; seven had moved overseas, nine refused follow up, and 43 were either untraced or unable to keep their appointment (47 of these 59 were subsequently seen at 18 months, when 96% of survivors were seen).

There were no significant differences between feed groups in follow up rate, mean length of gestation, birth weight, size for gestational age, sex distribution, Apgar score at five minutes, the proportion of infants requiring mechanical ventilation for 24 hours or more, social class, mother's education, or the infant's birth rank (data for a selection of these factors are shown in table 1). The median number of days (lower and upper quartile) to discontinuation of the assigned diet for infants fed donor milk (as sole diet or supplement) were 31 (22, 49), and the corresponding values for infants fed preterm formula were 28 (19, 40). There was no significant difference in the percentage of supplement received between infants fed formula or donor milk, 43·8% compared with 51·3%, respectively (SD 36%).

The numbers of infants in each group diagnosed as neurologically normal, equivocal, or impaired are shown in table 2. There are no significant differences in the incidence of neurological impairment.

Table 3 shows mean developmental scores for all five fields of development and for overall developmental quotient in the randomised comparisons. These data do not include scores for neurologically impaired infants, which are considered separately.

When the two trials were combined the infants

Table 1 *Comparison of preterm infants randomly assigned to receive banked breast milk or preterm formula as sole diet or as supplements to their mothers' milk*

	As sole diet		*As supplement to their mothers' milk*	
	Banked breast milk	*Preterm formula*	*Banked breast milk*	*Preterm formula*
No randomised	83	76	170	173
No who died before the age of 9 months*	7	9	12	15
No (%) seen nine months after the expected date of delivery	66/76 (87)	56/67 (84)	140/158 (89)	138/158 (87)
Characteristics of infants seen at nine months:				
Mean (SD) gestational age (weeks)	31·2 (2·8)	30·8 (2·8)	30·9 (2·7)	30·9 (2·4)
Mean (SD) birth weight (g)	1392 (298)	1364 (300)	1385 (297)	1386 (275)
No (%) weighing <1200 g at birth	18 (27)	17 (30)	36 (26)	38 (28)
No (%) small for gestational age†	24 (36)	20 (36)	37 (26)	49 (36)
No (%) boys	31 (47)	26 (46)	75 (54)	84 (61)
No (%) from social classes I, II or III non-manual	14 (21)	14 (25)	49 (35)	54 (39)
No (%) ventilated >1 day	27 (41)	27 (48)	51 (36)	55 (40)
Median (quartiles) No of days to full feeds	6 (5.8)	9 (6.16)	6 (5.9)	8 (6.10)

*Fifteen of the 43 deaths occurred before enteral feeds had been started. †birth weight less than 10th centile.

Table 2 *Neurological status, at nine months and at 18 months after the expected date of delivery assessed without knowledge of the feeding regimen by the methods of Amiel-Tison and Grenier*[16]

	As sole diet		*As supplement to their mother's milk*	
	Banked breast milk	*Preterm formula*	*Banked breast milk*	*Preterm formula*
Total assessed for impairment	66	56	140	138
At nine months:				
Impaired	4	8	7	12
Equivocal	0	1	8	3
Total	4	9	15	15
Impaired at 18 months	4	7	11	10

Table 3 *Developmental scores at nine months after the expected date of delivery for infants born preterm who had been randomly assigned during the early weeks after birth to receive banked breast milk or preterm formula as: sole diets or supplements to mothers milk (trials 1 and 2 combined); as sole diets (trial 1); or as supplements to their mothers' milk (trial 2). Data include overall developmental quotient and scores for five individual fields of development, expressed as mean (SD) with 95% confidence intervals for benefit from preterm formula*

	Banked breast milk	*Preterm formula*	*Difference—95% confidence interval*
Trials 1 and 2 combined:			
No of infants	195	174	
Overall developmental quotient	97·9 (9·6)	100·4 (10·7)	0·4 to 4·6**
Adaptive	101·3 (11·1)	104·0 (11·6)	0·4 to 5·1**
Gross motor	99·9 (17·2)	102·3 (17·7)	−1·2 to 5·9
Fine motor	96·6 (12·2)	99·2 (13·5)	0·0 to 5·3*
Language	93·3 (10·0)	95·6 (12·4)	0·0 to 4·6*
Personal-social	98·0 (11·4)	100·6 (12·6)	0·2 to 5·1*
Trial 1—Banked milk compared with preterm formula as sole diets:			
No of infants	62	48	
Overall developmental quotient	97·2 (8·5)	98·2 (11·0)	−2·7 to 4·8
Adaptive	99·5 (10·2)	101·6 (10·5)	−1·8 to 6·0
Gross motor	98·9 (16·2)	98·7 (15·2)	−6·2 to 5·6
Fine motor	95·2 (11·0)	97·1 (14·5)	−3·1 to 6·8
Language	93·8 (11·0)	95·2 (15·0)	−3·7 to 6·4
Personal-social	98·5 (8·5)	98·5 (11·0)	−4·7 to 4·6
Trial 2—Banked milk compared with preterm formula as supplements:			
No of infants	133	126	
Overall developmental quotient	98·2 (10·1)	101·2 (10·5)	0·5 to 5·6**
Adaptive	102·1 (11·4)	105·0 (11·9)	0·0 to 5·7*
Gross motor	100·4 (17·7)	103·7 (18·4)	−1·2 to 7·7
Fine motor	97·2 (12·8)	100·0 (13·1)	−0·3 to 6·0
Language	93·1 (9·6)	95·8 (11·3)	0·1 to 5·3*
Personal-social	97·7 (11·6)	101·5 (12·2)	0·8 to 6·6**

Data from infants with neurological impairment are excluded here and reported separately in the text (*=p<0·05, **p<0·025).

receiving preterm formula, either as sole diet or as supplement to their mothers' milk, had higher mean scores in all areas of development than those given donor milk as sole diet or supplement. Significant differences were seen in adaptive, fine motor, language, and personal-social areas, as well as in overall developmental quotient (95% confidence interval (CI) for difference: 0·4 to 4·6, p<0·02).

None of the differences seen between those infants receiving either donor breast milk or preterm formula as sole diet (the smaller of the two trials) reached significance, though there was a trend in favour of the preterm formula. In the larger group of infants whose mothers chose to provide breast milk, however, those supplemented with formula had higher mean scores in all areas of development than those supplemented with donor milk. The differences were significant in adaptive, language, and personal-social scores, also in overall developmental quotient where a three point advantage (95% CI 0·5 to 5·6, p<0·02) is seen for formula fed

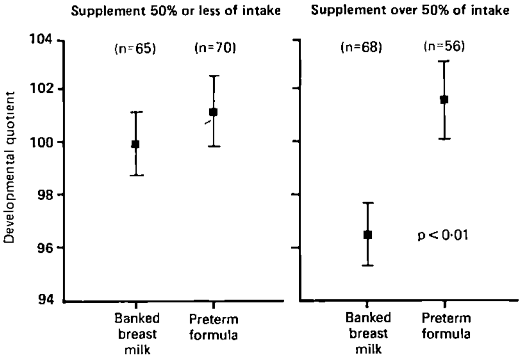

Fig 1 *Mean developmental quotient at nine months after the expected date of delivery in preterm infants randomly assigned to receive either banked breast milk or preterm formula as supplements to their mothers' milk. Mean (SEM) values from babies for whom this supplement was 50% or less of intake are shown on the left, and for those for whom it was over 50% are shown on the right.*

infants. In this 'supplement trial', however, mothers provided varying proportions of their infants' milk volume requirements. When mothers provided most of the infants' feed volume, the nature of the randomly assigned supplement could not be expected to make a major difference to outcome. Thus any difference in outcome between donor milk and preterm formula given as supplements to maternal milk would be blunted. We planned in advance therefore to analyse the results separately for infants of mothers providing up to half of the enteral intake and those whose mothers provided more than half. As expected, developmental advantages for infants given preterm formula rather than banked milk were greater for those infants where the supplement comprised more than half of their milk volume requirement, with a 4·9 point advantage in developmental quotient for those receiving the formula rather than donor milk (101·4 (SD 10·5) compared with 96·5 (9·9), $p<0·01$) (fig 1 and table 4).

Infants with neurological impairments (n=31) were considered separately. For those fed donor milk compared with formula as sole diets or supplement the mean (SE) developmental quotients were 74·4 (4·0) and 79·3 (4·9), respectively.

A birthweight cut off of 1200 g was used for stratifying the randomisation, after we had established from local statistics that this figure was the watershed for prognosis. The developmental advantage for infants fed preterm formula, however, was equal above or below this value.

SUBGROUP ANALYSES

To investigate whether associations between diet and development were more evident in some subgroups, further analyses of the data were undertaken. For these analyses both trials were combined (preterm formula compared with banked milk as sole diets or supplements to mothers' milk). Subgroups investigated were: infants whose birth weights were appropriate for gestational age compared with those who were small for gestational age (less than the 10th centile), girls compared with boys, and those ventilated for less than 24 hours compared with those ventilated for 24 hours or longer.

The results are shown in fig 2 and table 5.

Table 4 *Mean (SD) developmental scores and 95% confidence intervals for the advantage of infants fed preterm formula rather than banked breast milk as supplements to their mothers' milk, in those infants in whom this supplement was more than half of the total intake*

	Banked breast milk (n=68)	*Preterm formula (n=56)*	*95% confidence interval for advantage of preterm formula*
Overall developmental quotient	96·5 (9·9)	101·4 (10·5)	1·3 to 8·5***
Individual subscales:			
Adaptive	100·2 (10·7)	103·7 (10·5)	−0·2 to 7·2
Gross motor	98·3 (19·0)	103·7 (18·0)	−1·6 to 12·4
Fine motor	95·2 (13·2)	100·3 (13·5)	0·4 to 9·8*
Language	92·9 (9·1)	97·1 (11·2)	0·6 to 7·8**
Personal-social	96·5 (9·9)	101·4 (11·2)	1·7 to 9·3***

*=$p<0·05$; **$p=<0·025$; ***$p=<0·01$.

Table 5 *Mean (SD) developmental scores and 95% confidence interval for the advantage in small for gestational age infants fed preterm formula rather than banked breast milk*

	Banked breast milk (n=62)	*Preterm formula (n=68)*	*95% confidence interval for benefit of preterm formula*
Overall developmental quotient	94·3 (8·7)	99·6 (10·7)	2·0 to 8·6***
Individual subscales:			
Adaptive	96·7 (11·8)	103·8 (12·4)	2·9 to 11·1***
Gross motor	94·9 (17·3)	102·5 (18·1)	1·4 to 13·5**
Fine motor	92·8 (9·4)	99·3 (14·0)	2·2 to 10·2***
Language	91·7 (7·4)	92·2 (9·9)	−2·9 to 3·1
Personal-social	95·5 (11·0)	99·9 (12·4)	0·0 to 8·1*

*=$p<0·05$; **$p=<0·025$; ***$p=<0·01$.

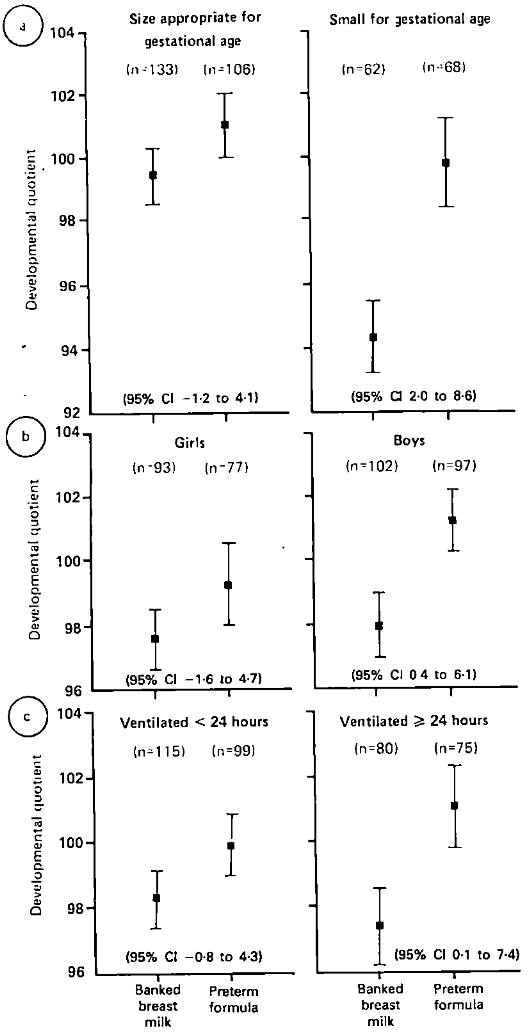

Fig 2 *Mean developmental quotient at nine months after the expected date of delivery in preterm infants randomly assigned to receive either banked breast milk or preterm formula as sole diets or supplements to their mothers' milk. Values shown as mean (SEM) and 95% confidence intervals (CI) are given for the differences: (a) size appropriate for gestational age (left), and small for gestational age (right); (b) girls (left), and boys (right); and (c) ventilated <24 hours (left), and ventilated ≥24 hours (right).*

Birth weight appropriate for gestational age compared with small for gestational age

The strongest association between diet and developmental quotient was seen in infants who were small for gestational age (<10th centile) fig 2(a), table 5). In this group there was a 5·3 point disadvantage ($p<0{\cdot}005$) in overall mean developmental quotient for those fed banked milk rather than preterm formula. The disadvantage of donor milk in babies small for gestational age (trials 1 and 2 combined) is shown for each individual subscale in table 5; significant disadvantages were seen for adaptive, gross motor, fine motor, and personal-social scores, the greatest being a 7·6 point disadvantage on the gross motor scale ($p<0{\cdot}02$). There was significant interaction between these dietary effects and fetal growth retardation in the adaptive ($p<0{\cdot}01$), gross motor ($p<0{\cdot}05$), and fine motor ($p<0{\cdot}01$) scores, and for overall developmental quotient ($p<0{\cdot}05$), showing that infants did indeed have a significantly greater developmental disadvantage on donor milk if they were small, rather than appropriate in size for gestational age.

Interestingly, infants receiving donor milk showed significant disadvantages in all fields of development except language after fetal growth retardation (table 5), whereas in infants of appropriate birth weight for gestational age the only significant disadvantage (not depicted) was seen on the language subscale (donor milk: 93·9 (11·0) compared with preterm formula: 97·8 (13·4)) ($p<0{\cdot}02$). In this field there was also some evidence of interaction between diet and whether or not the infant's growth was retarded ($p=0{\cdot}09$).

Boys compared with girls

Boys given preterm formula had a 3·3 point advantage in development quotient (95% CI 0·4 to 6·1), whereas girls had a smaller 1·7 point advantage (95% CI 1·6 to 4·7) (fig 2(b)). A significant interaction between the dietary effects and sex of the infant was not found, however.

Neonatal ventilation

In infants ventilated for less than 24 hours there was no significant association between diet and developmental quotient, whereas those infants ventilated for 24 hours or more had a mean quotient which was 3·7 points higher if they received the formula rather than donor milk (95% CI 0·1 to 7·4) (fig 2(c)), with a 6·2 point advantage in language development (95% CI 2·4 to 10·0, $p<0{\cdot}002$). In language development there was a significant interaction ($p<0{\cdot}01$) between the diet and whether the baby required mechanical ventilation for 24 hours or more.

Discussion

We have tested whether early diet influences neurodevelopment in man in a large, randomised, prospective trial of feeding in preterm infants. We found that the diet assigned during the early weeks after birth had a significant effect on developmental status nine months after the expected date of delivery. Infants fed a special cows' milk based preterm formula, had a significantly higher overall developmental quotient (when assessed by someone who was unaware of the randomisation) than those fed banked donor breast milk, when these diets were used alone and in combination with mothers' expressed milk. Though preterm formula feeding was associated with particular advantages in certain fields of development and subgroups of infants, in no specific instance was there any advantage for donor breast milk. These data have important biological implications and are pertinent to the long standing debate on whether unfortified mature human milk meets the nutritional requirements of premature babies.[13]

The developmental screening inventory of Knobloch *et al* that was used in this study consists of selected items from the Gesell developmental schedules.[16] When Gesell developmental quotient and Stanford-Binet intelligence quotient at school age are compared, the Pearson correlation coefficient (r) is 0·70, rising to 0·84 after weighting for socioeconomic state and incidence of convulsive seizures.[16] We expect that the correlation between mean development quotient and later mean intelligence quotient in randomised groups may be even better than correlations based on individuals. The longer term significance of our findings, however, is to be assessed at future follow up throughout childhood and beyond.

In trial 1, banked milk and preterm formula were assigned randomly as sole diets; in trial 2, they were given as supplements to the mothers' expressed breast milk (in volumes according to maternal success in providing sufficient milk to meet the infants' total feed volume requirement). Because in both trials the dietary assignment was random, demographic and clinical factors other than diet were equally represented between the two groups. Moreover, the combination of trials 1 and 2 was a balanced addition so that banked milk (as sole diet or supplement) compared with preterm formula (as sole diet or supplement) was still a randomised comparison.

We suggest that the observed significant differences in developmental scores between randomised diet groups are biologically important. Unlike intelligence quotient, the overall standard deviation for developmental quotient at nine months was only 10 points. In the whole cohort the overall disadvantage in developmental quotient on donor milk was 0·25 SD and in several major subgroups (see below) this disadvantage was 5 to 8 points (>0·5 SD). Although other factors (such as very low gestational age or severe respiratory disease) are associated with larger differences in developmental status at this age, diet is one of the few potential influences on development that can be manipulated in clinical practice.

Given that donor breast milk conferred a later developmental disadvantage overall, it was surprising that no significant differences were found in the comparison of banked donor breast milk or preterm formula as sole diets (trial 1). This was the smaller of the two trials, however, and the trend was generally towards a reduced developmental quotient on donor milk. The randomised comparison between donor milk and preterm formula as supplement to mother's milk, based on a much larger sample, showed a significant developmental disadvantage for the infants fed on donor breast milk. In infants whose mothers provided their own milk, the developmental disadvantage for those receiving donor milk rather than preterm formula as a supplement was greater when the intake of supplement was more than half the feed volume requirements. This 'dose response' association further supports the evidence for an early dietary effect on development.

In addition to effects of diet on overall developmental quotient, the randomised groups (trials 1 plus 2) differed significantly in performance on four of the five individual subscales (adaptive, fine motor, language, and personal-social skills) but not in gross motor skills. The standard deviation on the gross motor score, however, was large (table 3), suggesting that preterm infants are selectively damaged in this respect, and a large population would have been required to detect a diet related difference in this subscale. Nevertheless, gross motor scores were significantly influenced by diet in infants born with retarded growth.

Prenatal and neonatal malnutrition have each been shown to be associated with a 15% reduction in the total number of brain cells in rats; yet when 'doubly deprived', with both prenatal and postnatal malnutrition, they suffered a 60% reduction in the total number of brain cells by the time of weaning.[17] Though such data have uncertain relevance to man, we speculate that the infants in this study who were small for gestational age could be regarded as doubly deprived if, after intrauterine growth retardation, they were then fed an 'unfortified' diet such as banked breast milk (as a sole diet or supplement to maternal milk). Our previous studies[13] have indicated that human milk did not support intrauterine rates of somatic or head growth during the neonatal period, even in infants of normal birth weight, and certainly did not provide adequate nutrition for catch up growth in most of the infants born after growth had been retarded.

The significant interaction between diet and fetal growth retardation for developmental outcome indicates that infants in whom growth is retarded are especially vulnerable to postnatal undernutrition. Preterm formula fed infants had similar developmental quotients whether they were small or of appropriate size for gestational age, whereas infants fed donor milk were at a significant disadvantage if they were in the small for gestational age subgroup (fig 2(a)). Thus our data indicate that even with modern neonatal care, with emphasis on providing early nutrition, some available dietary regimens (especially when fed to neonates who are small for gestational age) may not permit achievement of full developmental potential in infancy.

Smart points out that in animal studies on undernutrition the effects on subsequent growth and behaviour are generally more pronounced in males than in females.[18] Interestingly, we showed a greater dietary association with development in male children. Furthermore, sick infants who were ventilated for more than 24 hours showed a greater disadvantage on donor breast milk than those receiving minimal or no ventilatory assistance. For these differential effects on development to have more than speculative importance it would be necessary to show significant interactions between diet and sex, or diet and ventilation. We identified a highly significant interaction between diet and ventilation for language development (sick ventilated infants on donor milk showed a 6·2 point disadvantage). For overall developmental quotient, however, significant interactions with diet were not identified for either sex or ventilation, though to exclude such effects would have required a much larger number. Nevertheless, the consistency of the data with those in animals, together with the more convincing findings in infants whose growth was retarded, supports the view that it is the 'vulnerable' male infant who is prenatally malnourished, or sick, who is most severely disadvantaged if fed on an 'unfortified' diet.

Our multicentre study should be viewed as a group of 'management trials'. They were designed to answer the question: does the diet chosen for a preterm infant in the neonatal unit influence long term outcome? No attempt has been made to influence dietary management in the time period between discharge from the neonatal unit and the follow up examination. As the groups were assigned randomly, differences in feeding practice in this intervening period should not have occurred unless part of the effect of the initial diet was to induce some persistent change influencing the way the baby was subsequently fed.

Viewed solely as a management trial our study should not be expected to provide an explanation for any benefit in outcome that emerged. We have included a number of physiological and behavioural studies within these trials and our future analyses may shed light on the mechanisms responsible for observed outcomes. It seems plausible, however, that the developmental effects observed were a direct consequence of early nutrition, perhaps relating to an important dietary influence on early head, and therefore brain, growth.[13] [19] The explanation might, however, have been entirely different; for instance, the faster growth rate[13] and hence earlier discharge home in preterm formula fed infants could have influenced the mother's behaviour towards the child, with consequent effects on development. It should be emphasised that donor milk and preterm formula differ both in nutrient and non-nutrient contents; an overall advantage for preterm formula may represent the sum of both benefits and disadvantages. Whether breast milk would confer a significant benefit over preterm formula if fortified to the same nutrient content is an important question requiring a further outcome trial. Regardless of the mechanism, it was surprising that a brief period of dietary manipulation (median 30 days) could have such prolonged consequences. It is unlikely that a comparable period of suboptimal nutrition in later childhood would have any lasting clinical significance. We suggest that the weeks immediately after birth constitute a 'critical period' for nutritional management.

The effects of early diet on later development shown in these infants have important implications for the dietary management of low birthweight infants, and bear on the more general issue of whether early diet has persistent neurodevelopmental consequences in man. Clearly future planned follow up of this cohort will permit us to examine the significance of our observations in terms of later performance.

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References

[1] Smart JL, Dobbing J, Adlard BPF, *et al.* Vulnerability of developing brain: relative effects of growth restriction during the fetal and suckling periods on behaviour and brain composition of adult rats. *J Nutr* 1973;**103**:1327–38.

[2] Stewart CA. Weights of various parts of the brain in normal and underfed albino rats at different ages. *J Comp Neurol* 1918;**29:** 511–28.

[3] Siassi F, Siassi B. Differential effects of protein-calorie restriction and subsequent repletion on neuronal and nonneuronal components of cerebral cortex in newborn rats. *J Nutr* 1973;**103:** 1625–33.

[4] Widdowson EM, McCance RA. Some effects of accelerating growth. I. General somatic development. *Proc R Soc Lond* 1960;**152:**188–206.

[5] Bedi KS, Thomas YM, Davies CA, Dobbing J. Synapse-to-neuron ratios of the frontal and cerebellar cortex of 30-day-old and adult rats undernourished during early postnatal life. *J Comp Neurol* 1980;**193:**49–56.

[6] Smart JL. Early life malnutrition and later learning ability: a critical analysis. In: Oliverio A, ed. *Genetics, environment and intelligence.* Amsterdam: Elsevier, 1977:215–35.

[7] Winick M. *Malnutrition and brain development.* Oxford: Oxford University Press, 1976:115.

[8] Chavez A, Martinez C. Neurological maturation and performance on mental tests. Quoted in: *Early nutrition and later achievement.* London: Academic Press, 1987:138–9.

[9] Freeman HE, Klein RE, Townsend JW, *et al.* Nutrition and cognitive development among rural Guatemalan children. *Am J Public Health* 1980;**70:**1277–85.

[10] Sinisterra L. Studies on poverts, human growth and development: the Cali experience. In: Dobbing J, ed. *Early nutrition and later development.* London: Academic Press, 1987:208–33.

[11] Klein PS, Forbes GB, Nadar PR. Effects of starvation in infancy (pyloric stenosis) on subsequent learning abilities. *J Pediatr* 1975;**87:**8–15.

[12] Ankett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child* 1986;**61:**849–57.

[13] Lucas A, Gore SM, Cole TJ, *et al.* Multicentre trial on feeding low birthweight infants: effects of diet on early growth. *Arch Dis Child* 1984;**59:**722–30.

[14] Office of Population Censuses and Surveys. *Classification of occupations 1980.* London: HMSO, 1980.

[15] Knobloch H, Pasamanick B, Sherard ES. A developmental screening inventory for infants. *Pediatrics* 1966;**38:**1095–108.

[16] Ameil-Tison C, Grenier G. *Neurological assessment during the first year of life.* Oxford: Oxford University Press, 1986.

[17] Minkowski A, Roux J-M, Tordet-Caridroit C. Pathophysiologic changes in intrauterine malnutrition. In: Winick M, ed. *Nutrition and fetal development.* Vol 2. New York: John Wiley, 1974:45–55.

[18] Smart JL. Undernutrition, learning and memory: review of experimental studies. In: Taylor TG, Jenkins NK, eds. *Proceedings of XIII International Congress of Nutrition.* London: Libbey, 1986:74–8.

[19] Cooke RWI, Lucas A, Yudkin PLN, Pryse-Davies J. Head circumference as an index of brain weight in the fetus and newborn. *Early Hum Dev* 1977;**1:**145–9.

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Bone mineral content and body size 65 to 100 weeks' postconception in preterm and full term infants

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SUMMARY A total of 36 preterm and 22 full term infants were weighed and measured at 65 to 100 weeks' postconception. It was found that the preterm infants were on average significantly lighter by 1008 g and shorter by 3·8 cm than those born at full term. Despite the smaller size of preterm infants, mean values of bone mineral content in the mid-forearm were not significantly different between the two groups. In contrast, near 40 weeks' postconception the mean bone mineral content observed in 35 of the preterm infants was significantly smaller than that observed in eight of the full term infants.

Our results suggest that there is a phase of rapid mineral accretion between 40 and 60 weeks' postconception. This 'catch up' in mineral accretion reduces the perinatal mineralisation deficit that might otherwise persist into childhood.

In most preterm infants, by 40 weeks' postconception there is a substantial deficit in bone mineral accretion relative to full term infants observed at birth.[1 2] Application of single photon absorptiometry to the mid-forearm has shown that those most seriously affected are infants born with extremely low birth weight (that is, <1000 g)[3]; by 40 weeks their bone mineral content is lower by about 35% after accounting for reduced weight and crown-heel length.[2] Preterm infants with higher birth weights are similarly undermineralised by about 20%.[1]

Attempts to accelerate postnatal mineral accretion in preterm infants have had variable success (unpublished observations).[4 5] Radiographically detectable osteopenia has reportedly been ameliorated by vitamin D supplementation.[6] Our own measurements, however, did not show more rapid mineral accretion in preterm infants when the daily vitamin D_2 intake was raised from the standard 400 IU to 1000 IU (unpublished observations). There is stronger evidence that the rate can be increased by mineral supplementation,[4 7] but the response is dependent on the way the supplement is administered, its amount, and whether or not vitamin D extra to the standard daily supplement is added.[4] Our results using mineral supplemented formula feeds showed a significant improvement in accretion rate up to 40 weeks' postconception[8]; however, by 40 weeks the preterm infants were still undermineralised relative to full term peers.

The thrust of supplementation studies towards restoration of mineral accretion rate to its in utero values arises partly from the desire to minimise known complications of neonatal osteopenia. It is not known, however, whether this is simply a short term problem or whether it has a long term impact on skeletal development. The purpose of the present study was to compare weight, crown-heel length, and bone mineral content in preterm and full term infants 65 to 100 weeks' postconception in order to determine whether or not effects of prematurity were detectable beyond the neonatal period. Differences in weight gain and linear growth were anticipated and particular emphasis was therefore placed on the bone mineral measurements.[9 10]

Patients and methods

This study was authorised by the local ethics committee. In all, 58 infants born between May 1984 and February 1988 were examined. They were all white singletons whose parents gave informed consent for the investigations to be performed. Of the 58, 36 infants (18 of each sex) had been born prematurely and comprised the 'preterm group', group P. The remaining 22 (15 boys), who were born after approximately 40 weeks' gestation, comprised the 'full term group', group F, and served as controls.

Infants in group P had been born in or referred to our neonatal intensive care unit during a 30 month period commencing July 1984. While in the unit they had been included in studies of the efficacy of various feeding regimes in promoting bone mineral accretion during the neonatal period.[8] After discharge from the unit they all received conventional formula feeds.

Of the 22 full term infants in group F, nine had previously served as controls in another study when much younger, and participated in the present investigation because their parents were prepared to bring them from home for remeasurement. The other 13 infants were recruited from the local general paediatric ward and were measured while inpatients. They were selected initially on the basis of age and race from all cases presenting with acute non-serious illness who had no history or signs of bone, liver, or renal disease. Patients who had received medication that in any way might have influenced mineral metabolism were rejected, as were those who had not been born at full term (assessed from birth case notes) and those who were below the 10th centile for weight on standard charts.[11] With four exceptions, all the full term infants received formula feed from birth; the remainder were breast fed, with weaning commencing at about 3 months of age.

Gestational age (completed weeks), calculated from maternal menstrual history and confirmed by either external examination[12] or ophthalmoscopic examination of the lens,[13] had been documented in each case. For group P, gestational age ranged from 26 to 31 weeks with mean (SD) 28·5 (1·8) weeks and for group F ranged from 37 to 42 weeks with mean 39·3 (1·5) weeks.

On up to three occasions but usually two, near to 40 weeks' postconception and in the period 65 to 100 weeks' postconception, the bone mineral content (mg/cm) was measured at the middle of the forearm of each infant by photon absorptiometry as described in previous publications.[1 3] The radiation exposure involved in this procedure is very small, and only a narrow area of the forearm is irradiated during a scan; skin entrance dose is 0·03 mGy per investigation. Weight (g) and crown-heel length (cm) were usually measured whenever a scan was performed.

In the postconceptional age range 37 to 45 weeks, complete data (that is weight (W), crown-heel length (CHL), and bone mineral content (BMC)) were obtained in 34 of the 36 preterm infants comprising group P; one had no measurements taken in that period, and in one infant crown-heel length was not measured. Results obtained at that time ('term data') are denoted by W1, CHL1, and BMC1, with PA1 denoting postconceptional age. Eight randomly selected members of group P (five boys) were also scanned while attending outpatient clinics when aged between 46 and 53 weeks' postconception; the resulting 'intermediate data', denoted by W2, CHL2, BMC2, were complete except in one case in whom weight and crown-heel length were not measured on the day of that scan. All 36 infants in group P were later scanned in the period 68 to 101 weeks' postconception, again when they attended for outpatient review. In three infants, neither weight nor crown-heel length was measured on the day of the final scan. Results obtained at that later time ('endpoint data') are denoted by W3, CHL3, and BMC3.

Soon after birth, in the postconceptional age range 39 to 43 weeks, complete data (that is, W1, CHL1, and BMC1) were obtained in eight (four boys) of the 22 full term infants comprising group F. All 22 infants were later scanned in the period 65 to 102 weeks' postconception. The data obtained in that interval (W3, CHL3, and BMC3) were complete. None of the full term infants had measurements taken at intermediate times.

Descriptive statistics for the term, intermediate, and endpoint data are given in tables 1, 2, and 3 respectively.

STATISTICAL ANALYSIS

Calculations performed on the data included simple linear regression, F tests of the significance of the difference in slopes of regression lines,[14] and analysis of variance and covariance using type of birth

Table 1 *Descriptive statistics for observations of weight (W), crown-heel length (CHL), and bone mineral content (BMC) obtained around 40 weeks' postconception in both the preterm (P) and full term groups (F) (term data). PA denotes postconceptional age*

	PA1 (weeks)	*W1 (g)*	*CHL1 (cm)*	*BMC1 (mg/cm)*
Group P:				
Mean	40·4	2620	46·15	118·8
SD	1·6	739	4·14	41·3
Maximum	44·6	4005	52·90	224·0
Minimum	37·4	1270	38·70	65·0
No of subjects	35	35	34	35
Group F:				
Mean	41·0	3344	50·38	190·9
SD	1·2	401	1·33	20·4
Maximum	42·7	3885	52·50	216·0
Minimum	39·1	2795	48·60	165·3
No of subjects	8	8	8	8

Table 2 *Descriptive statistics for observations of weight (W), crown-heel length (CHL), and bone mineral content (BMC) obtained between 46 and 53 weeks' postconception in the preterm group (P) (intermediate data). No intermediate data on group F were available*

	PA2 (weeks)	*W2 (g)*	*CHL2 (cm)*	*BMC2 (mg/cm)*
Group P:				
Mean	49·6	4029	53·71	207·9
SD	2·8	701	3·71	44·5
Maximum	52·7	4850	59·00	286·3
Minimum	46·1	2950	48·80	155·7
No of subjects	8	7	7	8

Table 3 *Descriptive statistics for observations of weight (W), crown-heel length (CHL), and bone mineral content (BMC) obtained in the postconceptional age range 65–100 weeks approximately in both the preterm (P) and full term groups (F) (endpoint data)*

	PA3 (weeks)	*W3 (g)*	*CHL3 (cm)*	*BMC3 (mg/cm)*
Group P:				
Mean	86·2	8148	71·23	301·8
SD	7·9	1229	4·00	80·0
Maximum	101·0	10 750	78·50	490·3
Minimum	68·4	5150	60·90	184·9
No of subjects	36	33	33	36
Group F:				
Mean	77·2	8732	72·26	279·0
SD	11·3	1203	4·66	73·0
Maximum	101·5	11 300	85·00	390·9
Minimum	65·3	6900	64·50	174·1
No of subjects	22	22	22	22

(preterm, full term) as a factor. Multiple regression analysis including a dummy independent variable based on type of birth was used to fit parallel regression lines to the data where appropriate.[14] These techniques were applied using postconceptional age rather than time since birth as an independent variable. The resulting models can if necessary be used to predict the outcome of comparisons between preterm and full term infants of similar ages expressed as time since birth.

Standard errors are denoted throughout by SE. Where error limits bound a mean point value, SE refers to the standard error of the mean. Where error limits about a regression line are given, SE refers to the standard error of the estimated mean.

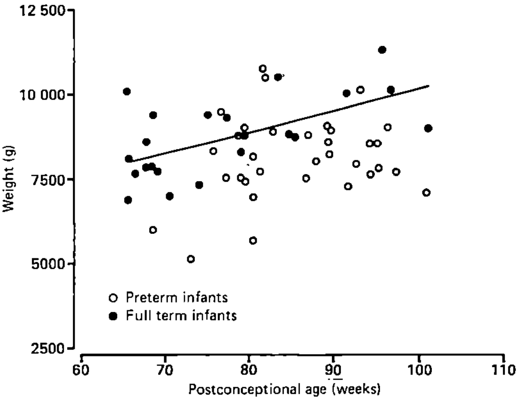

Fig 1 *The association between body weight and postconceptional age in preterm and full term infants (endpoint data). The regression line shown fits the data on the full term infants.*

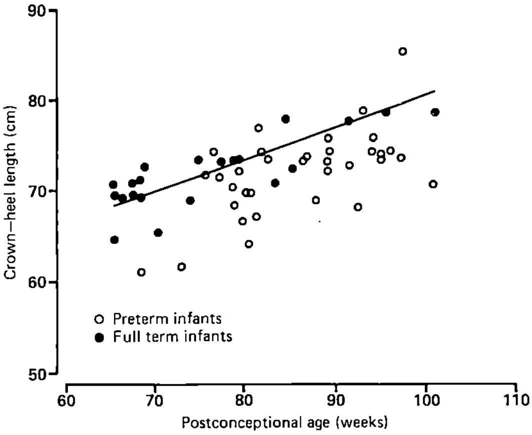

Fig 2 *The association between crown-heel length and postconceptional age in preterm and full term infants (endpoint data). The regression line shown fits the data on the full term infants.*

Results

Figs 1, 2, and 3 show the individual term data for weight, crown-heel length, and bone mineral content in relation to postconceptional age. Although in previous studies of younger infants it had been necessary to apply logarithmic transformations to all three measurements,[2 8 15] there was no evidence in the current endpoint data that such a transformation was necessary at these higher postconceptional ages. Linear regression analysis was therefore applied to the raw data, starting with the observations on the full term infants. The equations, correlation coefficients, and associated significance levels of the resulting regression lines shown in figs 1 to 3 were:

$W3 = 3873 + 62{\cdot}96\,{\cdot}PA3$ g $\quad r=0{\cdot}59,\ p<0{\cdot}005$
$CHL3 = 46{\cdot}00 + 0{\cdot}3402{\cdot}PA3$ cm $\quad r=0{\cdot}83,\ p<0{\cdot}001$
$BMC3 = -16{\cdot}80 + 3{\cdot}832\,{\cdot}PA3$ mg/cm $\quad r=0{\cdot}60,\ p<0{\cdot}005$

Preliminary inspection of the distributions of the observations on preterm infants relative to the regression lines shown in figs 1 and 2 indicated that weight and crown-heel length may be reduced in preterm infants relative to full term infants of comparable postconceptional age. In contrast, inspection of the results shown in fig 3 led us to conclude that there was no clear difference between values of bone mineral content in preterm and full term infants.

Regression analysis of the weight data for preterm infants shown in fig 1 resulted in a regression line having a slope not significantly different from the line illustrated. Analysis of variance and covariance showed type of birth (whether preterm or full term) to be a significant factor ($p<0{\cdot}005$) and multiple regression analysis was therefore performed using type of birth as a dummy variable. The two parallel lines which resulted are shown in the model illustrated in fig 4. The group centroid is indicated on each regression line; the ends of each line indicate the limits of the data. The common slope was 50·2 g/week (standard error of the slope, SES=16·4 g/week), the lower of the two intercepts was 3851 g and the difference of the intercepts was 1008 g (SE=341 g); the time separation of the two lines was therefore approximately 20 weeks. The multiple correlation coefficient was 0·44.

Similar analysis of the data for crown-heel length for preterm infants shown in fig 2 also resulted in a line with a slope not significantly different from the line illustrated, and analysis of variance and covariance again showed type of birth to be a significant factor ($p<0{\cdot}001$). The two parallel lines resulting from multiple regression analysis of the endpoint data are shown in the model illustrated in fig 5. Their common slope was 0·313 cm/week (SES=0·045 cm/week), the lower intercept was 44·50 cm and the difference of the intercepts was 3·76 cm (SE=0·935 cm); the time separation of the two lines was

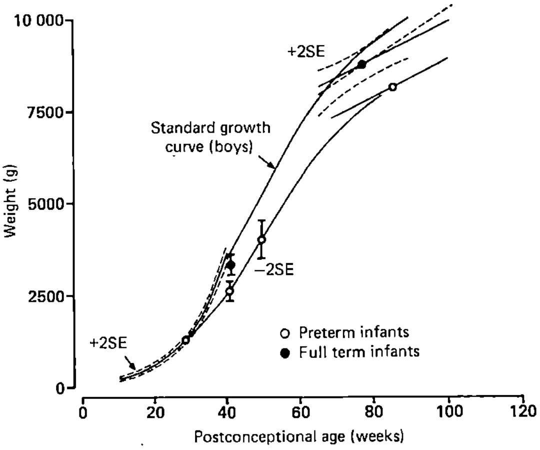

Fig 4 *Model of changes in weight with increasing postconceptional age in preterm and full term infants. SE denotes standard error of the mean for point values and standard error of the estimated mean for regression lines.*

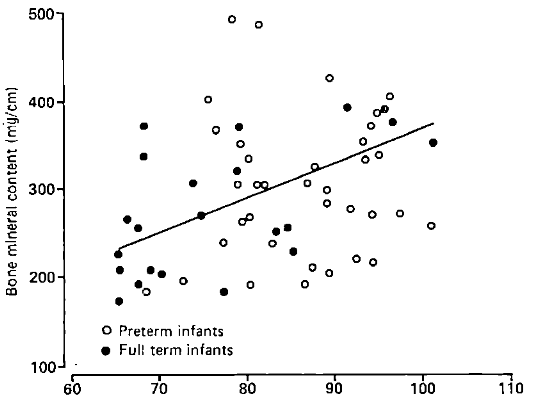

Fig 3 *The association between bone mineral content of the mid-forearm and postconceptional age in preterm and full term infants (endpoint data). The regression line shown fits the data on the full term infants.*

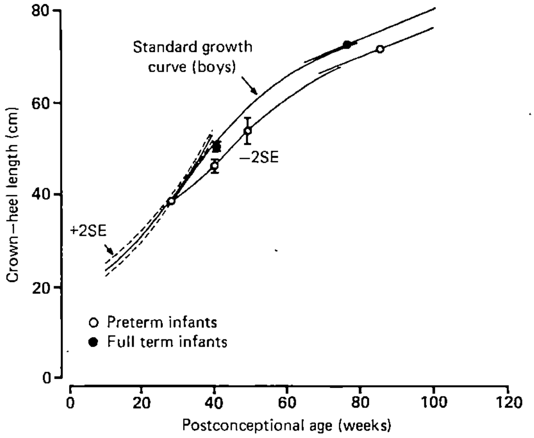

Fig 5 *Model of changes in crown-heel length with increasing postconceptional age in preterm and full term infants. SE denotes standard error of the mean for point values and standard error of the estimated mean for regression lines.*

approximately 12 weeks. The multiple correlation coefficient was 0.49.

Analysis of variance and covariance did not show type of birth to be a significant factor in the 'term data' for bone mineral content (fig 3) and a single regression line was therefore fitted to the combined observations on preterm and full term infants. That common line is shown in the model illustrated in fig 6. Its slope was 2·43 mg/cm/week (SES=0·96 mg/cm/week) and it passed through the value 286·8 mg/cm at 80 weeks' postconceptional age ($r=0{\cdot}32$; $p<0{\cdot}02$). The error bars drawn in fig 6 about the common line indicate the 2SE limits of the estimated mean (that is, the ordinate of the regression line at any postconceptional age).

Figs 4, 5, and 6 contain exponential curves from 10 to 40 weeks of age based on our previously published data on growth in utero[15]; 2SE limits of the estimated mean logarithmic values were computed at equally spaced intervals and antilogarithms taken to derive the error limits shown. In each figure the following are also included:

(1) A point on the in utero curve plotted at the mean gestational age of group P. This is the estimated mean value of the independent variable at birth for the preterm infants.

(2) The mean values with 2SE limits of the term data for groups P and F (from table 1). In the case of group F, infants with term data comprised only a small subset ($n=8$) of those with endpoint data ($n=22$).

(3) The mean value with 2SE limits of the intermediate data for group P (from table 2); again infants with those data comprised only a small subset ($n=7$ or 8) of those with endpoint data ($n=33$ or 36).

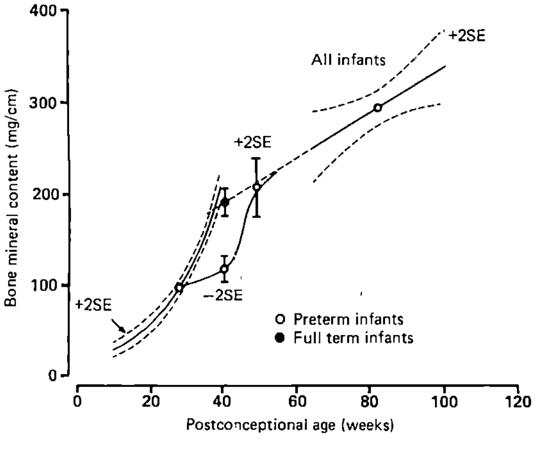

Fig 6 *Model of changes in bone mineral content of the mid-forearm with increasing postconceptional age in preterm and full term infants. SE denotes standard error of the mean for point values and standard error of the estimated mean for regression lines.*

(4) A smooth free hand curve joining the mean values described above for preterm infants with the regression line or lines representing the endpoint data for preterm infants.

For weight and crown-heel length, standard curves are available which describe the expected mean values from age 28 weeks onwards[11]; the standard weight curve for full term boys is shown in fig 4. The same figure also contains the regression line with its 2SE limits for the endpoint data on the full term group (dotted). In fig 5 the standard crown-heel length curve for boys is shown from 28 weeks.

Thus figs 4, 5, and 6 summarise how the *mean* values of weight, crown-heel length, and bone mineral content probably changed as postconceptional age increased in these groups of preterm and full term infants. In general terms, those figures should not be taken to describe the paths likely to be followed by any individual. For example, the paths followed by the individuals in the current study might have contained small plateau regions, not apparent in this set of data, that would only have been shown by frequently repeated sequential measurements throughout the whole age span.

Within the limitations of the available data, however, fig 4 clearly shows the sigmoidal shape of the growth curve for weight in both groups. Our in utero curve and the standard curve match up at 40 weeks; for the full term infants, the mean weight near to the time of birth, 3344 (284) g (2SE limits; 95% confidence interval is a factor of 1·18 greater), was consistent with the standard mean value of 3650 g approximately. The endpoint data on the full term infants were also consistent with the standard data for boys, the error limits of the regression line for full term infants (dotted) encompassing the standard curve. At all postconceptional ages group P had a lower mean weight than group F. For both the term data and intermediate data on group P, the mean value of weight was significantly lower than the standard value ($p<0{\cdot}001$), and the two parallel lines representing the endpoint data had significantly different intercepts ($p<0{\cdot}005$) as indicated above. The absolute mean weight difference between the groups increased with time, from about 700 g at 40 weeks to about 1100 g at 80 weeks. Relative to mean values in full term infants, these differences amounted to deficits of 21% and 13%. Viewing the two curves in fig 4 in a different way, the time lag between the two groups increased as postconceptional age increased: at about 40 weeks the preterm infants lagged behind the full term infants by about five weeks; around 80 weeks' postconception the preterm infants were about 20 weeks behind.

Fig 5 similarly shows the sigmoidal shape of the growth curve for crown-heel length in both groups. Our previously published regression equation describing length increase in utero systematically overestimated crown-heel length in the postconceptional age range 30 to 40 weeks; the standard curve in fig 5 lies below the exponential approximation to the in utero data. (The systematic error is evidence that the exponential approximation was invalid at the upper extreme of the age range examined.) With regard to the full term infants, the term data for crown-heel length (mean 50·38 (0·94) cm; 2SE limits) tended to be low but were reasonably consistent with the standard value (51·5 cm approximately). At higher postconceptional ages, the standard curve approached almost tangentially the upper of the two parallel regression lines describing the endpoint data. At all postconceptional ages, group P had lower mean values of crown-heel length than group F. For both the term data and intermediate data on group P, mean crown-heel length was significantly lower than the standard value ($p<0·001$ and 0·02 respectively), and the two parallel lines representing the endpoint data had significantly different intercepts ($p<0·001$) as mentioned above. The absolute difference between the groups in mean crown-heel length remained essentially constant from 40 weeks onwards at about 5 cm. Relative to values in full term infants, this amounted to a length deficit of about 10% at 40 weeks and 7% at 80 weeks. Again the time lag between the two groups increased as postconceptional age increased; at about 40 weeks the preterm infants lagged behind the full term infants by about five weeks; around 80 weeks' postconception the preterm infants were more than 10 weeks behind.

Fig 6 illustrates the divergence and reconvergence of the mean bone mineral content values in the preterm and full term groups. For group F, the mean value of the term data lay very close to the line produced by backward extrapolation of the regression line through the endpoint data, that is, it appears from these results that the rate of increase of bone mineral content in the full term infants was constant from birth onwards. The postnatal rate of mineral accretion was less than the rate appertaining in utero, even at the very lowest gestational ages investigated in previous studies. The mean value of bone mineral content for the term data (group F) was somewhat lower than the mean value predicted by the exponential in utero curve; this finding was anticipated on the basis of the rather low mean value of crown-heel length observed in this subset of the full term infants (fig 5). The mean value of the intermediate data for bone mineral content on the preterm infants lay close to the line joining the data on full term infants, implying that the deficit evident in the preterm infants at 40 weeks had been largely made up at 50 weeks' postconception. The mean values of the term data were significantly different between the two groups ($p<0·001$), as expected from previous studies[1 2]; near 40 weeks the mean value for group P was about 60% of the mean value for group F.

Discussion

Our weight and crown-heel length measurements are consistent with the common clinical observation that in the postconceptional age range 65 to 100 weeks, preterm infants are lighter and shorter than their full term peers.[9] In the groups we studied the weight deficit was about 1000 g and the crown-heel length deficit was about 4 cm.

Those results, coupled with previous observations in preterm infants of substantial deficits in bone mineralisation at about 40 weeks' postconception,[1 2] led us to expect that there might be a systematic, longer term mineralisation deficit in such cases. The null hypothesis tested in the analysis presented above was that no mineralisation deficit existed after 65 weeks' postconception, and contrary to expectations that hypothesis could not be rejected on the basis of the observations. Our present conclusion is therefore that we have no evidence of a longer term mineralisation deficit in preterm infants, despite their reduced body size, where mineralisation deficit here refers specifically to the mineral content of a 1·0 cm length of the mid-forearm, summated over the two bones.[3]

Although we and others have used that measurement to quantify osteopenia of prematurity in the neonate,[1 2 4 7] it would not be valid to conclude from the results of this study that osteopenia of prematurity has been shown to be a self remitting condition with no long term consequences for skeletal status in the broadest sense. Mineralisation of the forearm bones at their metaphyses, which were not monitored in our study, might be affected by prematurity; there may also be persistent effects of prematurity on mineral accretion at other skeletal sites that are not mirrored in changes at the mid-forearm site.[16]

Furthermore, as prematurity is clearly associated with changed bone morphology (that is, reduced length of the long bones), the rate of matrix synthesis must itself be reduced, perhaps with secondary effects on mineralisation. For example, the lack of a mineralisation deficit in the mid-forearm may be partly a consequence of the fact that linear growth is retarded in preterm infants, the available mineral supply being deposited in the diaphysis rather than in the metaphyses, because the latter grow less rapidly than they should in those cases. The bones of preterm infants are not only shorter; the distribution of mineral within the forearm bones appears to differ from that in full term infants. In such a situation, the limits of our present methodological approach have been reached, and future studies may need to include, for example, measurements of the length of the mineralised region in the radial diaphysis.

There are currently few published results with which our endpoint data can be compared. Although several groups have used peripheral absorptiometry to examine bone mineralisation in the first year of life,[9 16–24] currently no other published study has involved both preterm and full term infants in the postconceptional age range 65 to 100 weeks. Previously published data from Chan and coworkers on somewhat younger full term infants[23] and preterm infants,[17] who were rather heavier than our cases, however, are consistent with our findings. Comparison of their data from the two studies shows that by the postconceptional age of 56 weeks the mean value of bone mineral content observed in their preterm group (103 mg/cm) was similar to the mean value observed in their full term group (110 mg/cm).

If preterm and full term infants do in fact have very closely similar mean values of bone mineral content by about 60 weeks' postconception, yet differ substantially at 40 weeks, it is an obvious deduction that, in the interval 40 to 60 weeks, preterm infants must have a higher rate of mineral accretion than full term infants. Published data from several sources strengthen this conclusion and also highlight the large interindividual variability in the rate of mineral accretion. Between 40 and 56 weeks' postconception, preterm infants have been shown to increase their bone mineral content value by between 30% and 60% of the mean value observed in full term infants close to the time of birth.[9 17 18] Over the same period term infants have been shown to increase their bone mineral content values by smaller amounts, in the range 11 to 45%.[20 23]

Our observation of accelerated mineral accretion in the forearms of preterm infants between 40 and 60 weeks' postconception is therefore consistent with the findings of other workers. The acceleration appears to be of sufficient magnitude to reduce substantially the large mineral deficit which develops in preterm infants in the immediately postnatal period and which might otherwise persist into childhood. Detection of residual effects too small to be revealed by the current study would require a different experimental approach, perhaps involving radiography and frequent sequential observations of individuals throughout the whole span of postconceptional age under investigation.

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References

[1] James JR, Congdon PJ, Truscott J, Horsman A, Arthur R. Osteopenia of prematurity. *Arch Dis Child* 1986;**61**:871–6.

[2] Horsman A, Ryan SW, Congdon PJ, Truscott JG, James JR. Osteopenia in extremely low birthweight infants. *Arch Dis Child* 1989;**64**:485–8.

[3] James JR, Truscott J, Congdon PJ, Horsman A. Measurement of bone mineral content in the human fetus by photon absorptiometry. *Early Hum Dev* 1986;**13**:169–81.

[4] Steichen JJ, Gratton TL, Tsang RC. Osteopenia of prematurity; the cause and possible treatment. *J Pediatr* 1980;**96**:528–33.

[5] Gross SJ. Bone mineralization in preterm infants fed human milk with and without mineral supplementation. *J Pediatr* 1987;**111**:450–8.

[6] Seino Y, Ishii T, Shimotsuji T, Ishida M, Yabuuchi H. Plasma active vitamin D concentration in low birth weight infants with rickets and its response to vitamin D treatment. *Arch Dis Child* 1981;**56**:628–32.

[7] Greer FR, McCormick A. Improved bone mineralization and growth in premature infants fed fortified own mother's milk. *J Pediatr* 1988;**112**:961–9.

[8] Horsman A, Ryan SW, Congdon PJ, Truscott JG, Simpson M. Bone mineral accretion rate and calcium intake in preterm infants. *Arch Dis Child* 1989;**64**:910–8.

[9] Greer FR, McCormick A. Bone mineral content and growth in very-low-birth-weight premature infants. *Am J Dis Child* 1987; **14**:179–83.

[10] Karniski W, Blair C, Vitucci JS. The illusion of catch-up growth in premature infants. *Am J Dis Child* 1987;**141**:520–6.

[11] Gairdner D, Pearson J. A growth chart for premature and other infants. *Arch Dis Child* 1971;**46**:783–7. (Revised, Ware: Castlemead Publications, 1985.)

[12] Parkin JM, Hey EN, Clowes JS. Rapid assessment of gestational age at birth. *Arch Dis Child* 1976;**51**:259–63.

[13] Hittner HM, Hirsch NJ, Rudolph AJ. Assessment of gestational age by examination of the anterior vascular capsule of the lens. *J Pediatr* 1977;**91**:455–8.

[14] Armitage P. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, 1971.

[15] Ryan S, Congdon PJ, James J, Truscott J, Horsman A. Mineral accretion in the human fetus. *Arch Dis Child* 1988;**63**:799–808.

[16] Hillman LS. Bone mineral content in term infants fed human milk, cow milk-based formula, or soy-based formula. *J Pediatr* 1988;**113**:208–12.

[17] Chan GM, Mileur LJ. Posthospitalisation growth and bone mineral status of normal preterm infants. *Am J Dis Child* 1985;**139**:896–8.

[18] Abrams SA, Schanler RJ, Garza C. Bone mineralisation in former very low birth weight infants fed human milk or commercial formula. *J Pediatr* 1988;**112**:956–60.

[19] Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *J Pediatr* 1981;**98**:696–701.

[20] Roberts CC, Chan GM, Folland D, Rayburn C, Jackson R. Adequate bone mineralisation in breast-fed infants. *J Pediatr* 1981;**99**:192–6.

[21] Greer FR, Searcy JE, Levin RS, Steichen JJ, Steichen-Asche PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one year follow-up. *J Pediatr* 1982;**100**: 919–22.

[22] Chan GM, Leeper L, Book LS. Effect of soy formulas on mineral metabolism in term infants. *Am J Dis Child* 1987;**141**: 527–30.

[23] Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralisation of normal breast-feeding infants and the effects of lactation on maternal bone mineral status. *Am J Clin Nutr* 1982;**36**:438–43.

[24] Steichen JJ, Tsang RC. Bone mineralisation and growth in term infants fed soy-based or cow milk-based formula. *J Pediatr* 1987;**110**:687–92.

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Norrie's disease: a prospective study of development

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SUMMARY Developmental progress, hearing, and dysmorphic features were monitored prospectively in eight babies with Norrie's disease (an X linked form of congenital blindness believed to be associated with mental retardation, regression, sensorineural deafness, and dysmorphic features) and in six congenitally blind peers during their preschool years. No evidence of sensorineural deafness or dysmorphology was found in the group with Norrie's disease. No significant difference in the rate of developmental progress occurred between the two groups. All 14 children showed continuing developmental progress and in 10 this was at a normal or superior rate. Two cases and two controls showed slowing in their rate of progress; in both groups a suboptimal developmental climate had prevailed and may have been contributory.

The emphasis on serious and progressive associated disabilities in past reports has led to considerable distress for families of children with this disease. Our study suggests that these anxieties may often be illfounded. Parental depression constrains development, particularly when a baby is blind. More optimistic counselling with developmental guidance is recommended for children who are not overtly retarded in infancy until the long term developmental perspective of this disease is further clarified.

Norrie's disease is an X linked recessive condition of bilateral ocular malformation and blindness. Gordon Norrie (1927) identified nine Danish boys with 'atrophia oculi congenita'.[1] The eye looked as 'if it had decayed after a very serious process of inflammation'. In 1961 Andersen and Warburg proposed these cases of congenital bilateral pseudotumour of the retina should be named Norrie's disease.[2]

The initial ocular manifestation of Norrie's disease is a grey or greyish yellow tumour like mass (pseudotumour) behind both lenses. During the first few months of life, the lenses develop cataracts and the corneas progressively opaque. Ocular pathology includes haemorrhage, vitreous opacities, glaucoma, iris atrophy, and synechiae. Phthisis bulbi is present by the end of the first decade.

Blindness is usually total by the end of the neonatal period. A few children have preservation of light perception in the first few years. Warburg postulated that blindness in Norrie's disease is due to a developmental dysplasia of the retina, which leads to total retinal detachment and proliferation of retinal vessels.[3] The detached retina is seen behind the lens as a white vascular mass.

Family histories, when present, have suggested X linked inheritance.[2 4] Diagnostic difficulty arises in the absence of a family history as the retinal dysplasia is not specific for Norrie's disease. Recent genetic advances are likely to help with diagnosis in the future; the gene for Norrie's disease (NDP) is thought to be closely linked on the regional map to locus DXS7 which is defined by the probe L1.28.[5] Deletion of locus DXS7 has been reported in some recent cases of Norrie's disease.[6 7] A mother must be heterozygous for the L1.28 restriction fragment length polymorphism for the probe to be informative.

Sensorineural deafness has been reported in several studies of Norrie's disease.[8–11] Warburg found deafness in approximately a third of cases.[3] In her 1977 study, she proposed that hearing loss was progressive and appeared in early or middle childhood.[12] Deafness has been reported as early as 4 months of age.[13]

A characteristic Norrie's disease facies was described by Donnai *et al*[7]: with fine features, narrow nasal bridge, hypotelorism, flattened malar region, thin upper lip, and large ears. Microcephaly, cryptorchidism, and limb anomalies have also been described.[9 11] Clinicians have increasingly used evidence of deafness and dysmorphology as confirmatory criteria for diagnosis of Norrie's

Table 1 *Medical, social, and family background of children with Norrie's disease (a-h) and controls (A-F)*

Case	*Pregnancy and delivery*	*Gestation (weeks)*	*Birth weight (g)*	*Family history*	*Age at diagnosis*	*Diagnosis*	*Medical and social problems and dysmorphic features*
a	Normal pregnancy, caesarean section for transverse lie	41	3300		2 days 10 weeks	Congenital buphthalmos, Norrie's disease	Intermittent conductive hearing loss. Parental separation and divorce 1985–7
b	Normal pregnancy, forceps delivery for failure to progress	41	3000	Brother of case a	1 day	Norrie's disease	Social factors as above
c	Threatened miscarriage at 12 weeks treated with progestogens, forceps delivery	40	3520		2 days 8 weeks	Congenital buphthalmos Norrie's disease	
d	Normal pregnancy, normal delivery	40	3000	Brother of case c	1 day	Norrie's disease	
e	Pre-eclampsia, normal delivery	40	3400	Parents first cousins, two great uncles blind	8 weeks*	Norrie's disease	Severe eczema and asthma at 18 months, many hospital admissions
f	Normal pregnancy, normal delivery	40	4500		6 weeks*	Norrie's disease	
g	Normal pregnancy, normal delivery	40	2900		1 day (white mass right eye)	Norrie's disease	
h	Normal pregnancy, normal delivery	39	2600		6 weeks*	Norrie's disease	
A	Threatened miscarriage at 12 weeks, normal delivery	40	3000		1 day	Anophthalmos	Hospital admissions for wheezy bronchitis
B	Flu-like illness at 24 weeks, normal delivery	40	3000		6 months*	Hypoplastic optic discs, retinal aplasia	Severe social deprivation from 1·5 years; taken into foster care age 2·5 years
C	Normal pregnancy, normal delivery	40	2700		1 day	Anophthalmos	Jaundice, given phototherapy in 1st week of life
D	Normal pregnancy, caesarean section for fetal distress	41	3460	Parents first cousins	1 day	Anophthalmos	Pyloric stenosis at 3 weeks. Absent left index fingernail, widely spaced toes and nipples
E	Bleeding due to placenta praevia, caesarean section	38	2950	Parents first cousins	1 day	Anophthalmos	Bilateral syndactyly second and third toes, absent fifth toes; preauricular skin tag left ear
F	Small bleed at 12 weeks, normal delivery	40	3300		3 months	Hypoplastic optic discs	Jaundice, given phototherapy in 1st week of life. Glucose-6-phosphate dehydrogenase deficiency

*Not fixing or following.

disease.[7 10 11] Our clinical experience has led us to doubt the diagnostic status of these signs.

Mental retardation has been described in Norrie's disease. Warburg's study in 1966 is the main source of developmental knowledge on Norrie's disease. She looked at 35 cases consisting of children in institutions for the blind and cases found from retrospective data.[3] Sources included *The Index of Diagnoses of Ocular Diseases in Mentally Deficient Patients in Denmark* and a survey of blind adults in homes for the mentally deficient. Forty five per cent (16/35) were born before 1900 and documentation of early milestones and development is scanty. Warburg described normal development during the first two years of life in all boys.[3 14] Subsequent progress was then distributed equally between three categories. Development continued normally into adult life in approximately one third of cases. Slowing of development was noted in another third after the age of 2 years; they presented as moderately slow learners in their early school years but continued to lose skills in teenage and adult life. The remaining third regressed rapidly after the age of 2 years losing their previous skills. Our clinical experience led us to question the developmental perspective outlined by Warburg.

This study was undertaken to review early developmental patterns, sensorineural deafness, and dysmorphic features in Norrie's disease.

Subjects and methods

The diagnostic criteria for Norrie's disease applied in this study are a clinically compatible retinal dysplasia and total blindness present in the first few months of life coupled with negative history and investigation for alternative aetiological factors.

Development has been prospectively monitored in children with Norrie's disease and compared with the development of a control group blind from other causes. The study and control groups were derived from 345 children referred to the developmental vision clinic at the Wolfson Centre from 1975-86. Children referred to this specialised clinic are all severely visually impaired and often multiply disabled. Those with any residual sight after the first few months of life or a history of prematurity, congenital infection, 'brain damaging' events or abnormality on computed tomography were excluded. Eight cases fulfilled the above criteria for Norrie's disease. Six totally blind children fulfilled the criteria for the control group.

Assessments were performed at regular intervals by a psychologist and a paediatrician for children in both groups. The following details were recorded for each case: family history, physical features, and hearing and growth indices. Development was assessed on the Reynell-Zinkin developmental scales of young visually handicapped children, using the sensorimotor understanding and verbal comprehension subscales. Scores were compared with age equivalents for blind children derived from the standardisation sample of Reynell.[15] The progress of children after they reached the age of 5 years was monitored using the British ability scales, sighted norms.[16] The four subscales thought to be least affected by visual impairment—that is, verbal-tactile matching, recall of digits, verbal fluency, and similarities—were used. Hearing assessments were performed by distraction technique, discrimination of speech, free field audiometry, or audiometry with headphones as developmentally appropriate.

Results

There was no history of neonatal difficulties or medical history relevant to blindness in either group (table 1). A positive family history was obtained in five of the children with Norrie's disease: the parents of one child (case e) were first cousins and, therefore, had in common two great uncles who were blind but of normal development, and cases a and b and c and d were sibling pairs. There was no family history of blindness in the control group. Two sets of control parents were first cousins (of cases D and E) but blindness did not feature in any family. Dysmorphic features were noted in two of the control children (cases D and E) but none of the study group.

Hearing loss was detected in one child with Norrie's disease (case a) and in none of the controls. The loss in this case was conductive and had been intermittent, associated with flat impedance curves and dull eardrums on inspection. At 6·8 years of age, hearing was normal on the right and a 30 dB conductive loss was present on the left.

The developmental progress of study and control groups is shown in table 2 and figs 1–4. There was no

Table 2 *Developmental progress assessed on Reynell-Zinkin developmental scales*

		Sensormotor understanding		*Verbal comprehension*		
*Age band**	*Group*	*≥Blind norm*	*<Blind norm*	*≥Blind norm*	*<Blind norm*	*Total*
1	Norrie's	7	1	6	2	8
	Control	4	1	4	1	5
2	Norrie's	6	2	6	2	8
	Control	3	3	2	4	6
3	Norrie's	5	3	5	3	8
	Control	3	3	1	5	6
4	Norrie's	5	2	5	2	7
	Control	2	1	2	1	3
5	Norrie's	4	2	4	2	6

*Assessment closest to date of 1st, 2nd, 3rd, 4th, and 5th birthdays.

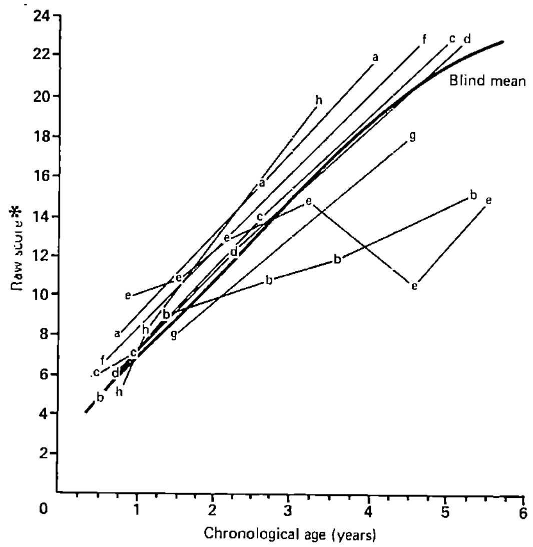

Fig 1 *Sensorimotor understanding in Norrie's disease. *Each item on this subscale of the Reynell-Zinkin developmental scale scores 1; the Raw score indicates the number of items achieved.*

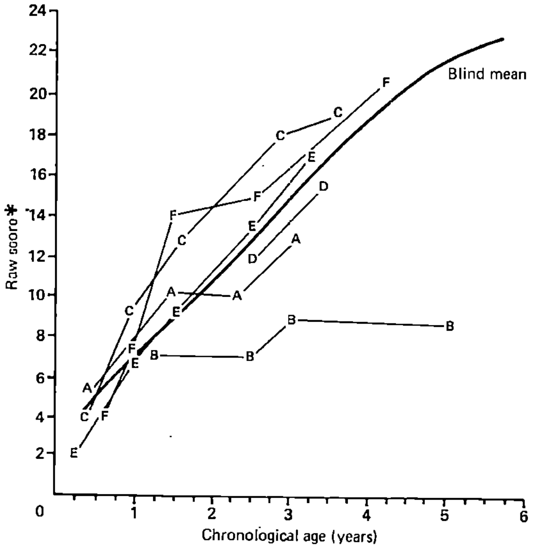

Fig 2 *Sensorimotor understanding in controls. *Each item on this subscale of the Reynell-Zinkin developmental scale scores 1; the Raw score indicates the number of items achieved.*

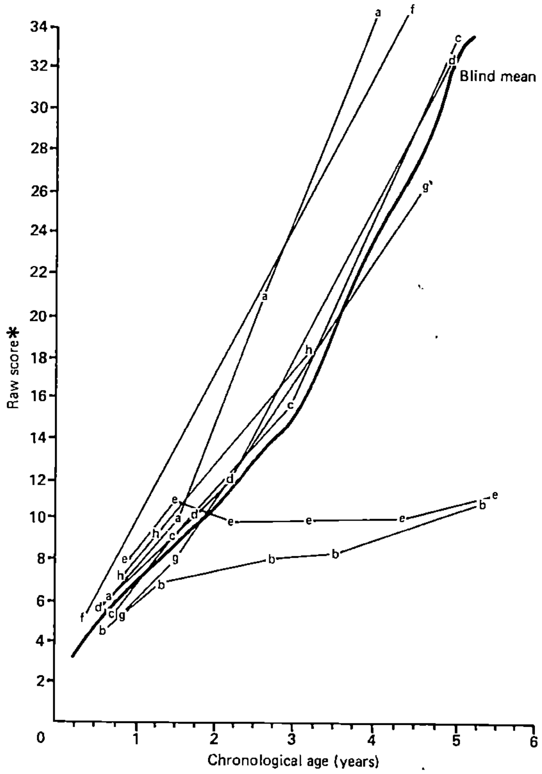

Fig 3 *Verbal comprehension in Norrie's disease. *Each item on this subscale of the Reynell-Zinkin developmental scale scores 1; the Raw score indicates the number of items achieved.*

significant difference in development between the two groups at any age (Fisher's test of exact probability). The only finding to approach significance was verbal comprehension at 3 years of age, where the difference was in the opposite direction to that expected from Warburg's retrospective data. Six children with Norrie's disease (75%) and four controls (66%) showed steady rates of development. In eight children (from both groups) this was at or above the blind 'norm'; in one child with Norrie's disease, and one control (cases g and D) this was just below the blind 'norm'. Four of the children with Norrie's disease (cases a, c, d, and f), who were recently reassessed on the British ability scales, scored in the above average range and two (cases a and f) in the superior range of norms for sighted children. Four children, equally divided between study and control groups (cases b, e, A, B), showed a plateauing in their developmental skills around the age of 2 years. At last assessment they would be described as mentally retarded. In both groups, regression or poor progress seemed to be associated with illness requiring frequent hospital admissions or social deprivation (table 2). All these children showed evidence of continuing development, although at a slower rate than normal.

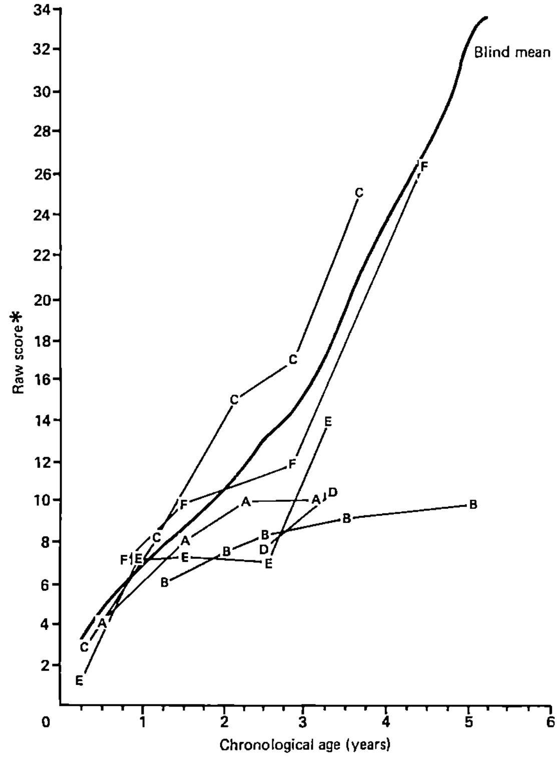

Fig 4 *Verbal comprehension in controls. *Each item on this subscale of the Reynell-Zinkin developmental scale score 1; the Raw score indicates the number of items achieved.*

Discussion

A conductive hearing loss was present in one child with Norrie's disease. There was no evidence of sensorineural hearing loss in the first five years among our sample of children. Our study does not confirm reports of early onset of sensorineural hearing loss. A developmentally age appropriate test was selected for each child in our study, thereby overcoming Warburg's difficulty in obtaining reliable hearing assessments in cases who were mentally retarded or unable to speak. Most hearing losses were identified in the third decade of life in Warburg's series so we propose to continue to monitor hearing prospectively in our group.

The characteristic facies described by Donnai *et al*[7] and other physical features such as cryptorchidism, microcephaly, and limb anomalies were absent in our series. Warburg did not discuss dysmorphic features in her description of Norrie's disease. When such features are associated with Norrie's type retinal dysplasia the explanation may lie in the width of the faulty gene segment of the X chromosome in the individual case.

Genetic considerations make precise diagnosis important. A female carrier of the Norrie's disease gene has a 50% chance of having an affected child if the fetus is male. Other ocular conditions that require to be differentiated are bilateral retinoblastoma, retinoschisis, falciform detachment of the retina, retrolental fibroplasia, and syndromes with retinal dysplasia.[17] Serial ocular examinations by a specialist during the early weeks of life facilitate the differential diagnostic process. Our findings suggest that diagnostic criteria should be primarily visual and ocular and not include the range of associated features such as mental retardation, dysmorphology, and hearing impairment. Total blindness by the age of a few weeks plus ocular signs compatible with a Norrie's retinal dysplasia together with exclusion of the other conditions mentioned above should at present be the essential criteria. A positive family history is strong supportive evidence but not essential.[17] The recent identification of the gene locus for Norrie's disease and the discovery of a suitable probe have made prenatal diagnosis possible.[6] Extension of the research is likely to clarify whether adjacent sites are abnormal in those cases with associated features and whether in such families they tend to breed true.

In the current study, prospective monitoring of early development in Norrie's disease has shown a different perspective to that described by Warburg. Most of these children are of normal ability when compared with their blind peers. Children with Norrie's disease were *not* more likely to be mentally retarded than controls. The two children who showed superior mentality at the age of over 5 years when assessed using the British ability scales (sighted norms) emphasise the existence of such a subgroup. Warburg reported that a third of children with Norrie's disease show regression of development during the preschool years. A quarter of our sample (cases b and e) showed plateauing followed by slow progress rather than further regression. Some of the difference in developmental perspective of the two series may reflect a sampling bias; the population of Warburg's series was drawn mainly from institutions for the blind and the data was mainly retrospective. Blind children are particularly susceptible to developmental stasis or regression if the developmental climate is suboptimal as a consequence of emotional deprivation or admission to hospital.[18] Such a climate prevailed in both study and control group children in whom such a pattern was seen.

The possibility that their son and future sons may not only be blind, but could develop further impairments such as mental retardation or deafness, greatly increases parental anxiety and distress. This concern will be mirrored in young couples related to the mother.[19] Warburg's 1966 review and recent case reports understate the cases who remain of average or superior intelligence throughout life,[7 9 13] and thus heighten rather than alleviate parental and professional despair about Norrie's disease. Despair and depression can reduce a mother's ability to interact and promote her baby's development—a developmental disaster for a blind baby.[20] Until further studies show the true long term perspective in this disease a more optimistic approach, coupled with a programme to promote development, is recommended as the wisest developmental counsel in cases who do not show overt retardation in the early months.

References

[1] Norrie G. Causes of blindness in children. *Acta Ophthalmol (Copenh)* 1927;**5**:357–86.

[2] Andersen SRM Warburg M. Norrie's disease. *Arch Ophthalmol* 1961;**66**:614–8.

[3] Warburg M. Norrie's disease: a congenital progressive occulo-acoustico-cerebral degeneration. *Acta Ophthalmol [Suppl] (Copenh)* 1966;**89**:1–147.

[4] Warburg M. Norrie's disease (atrofia bulborum hereditaria). *Acta Ophthalmol (Copenh)* 1963;**41**:134–46.

[5] Bleeker-Wagemakers LM, Friedrich U, Gal A, Wienker TF, Warburg M, Ropers HH. Close linkage between Norrie's disease, a cloned DNA sequence from the proximal short arm and the centromere of the X chromosome. *Hum Genet* 1985;**71**:211–4.

[6] De la Chapelle A, Sankila EM, Lindlof M, Aula P, Norio R. Norrie's disease caused by a gene deletion allowing carrier detection and prenatal diagnosis. *Clin Genet* 1985;**28**:317–20.

[7] Donnai D, Mountford RC, Read AP. Norrie's disease resulting from a gene deletion: clinical features and DNA studies. *J Med Genet* 1988;**25**:73–8.

[8] Liberfarb RM, Eavey RD, De long GR, Albert DM, Dieckert JP, Hirose T. Norrie's disease: a study of two families. *Ophthalmology* 1985;**92**:1445–51.

[9] Holmes LB. Norrie's disease. An X-linked syndrome of retinal malformation, mental retardation and deafness. *J Pediatr* 1971;**89**:89–92.

[10] Phillips CI, Newton M, Duvall J, Holloway S, Levy AM. Probable Norrie's disease due to mutation. *Br J Ophthalmol* 1986;**70**:305–13.

[11] Moreira-Filho CA, Neustein I. A presumptive new variant of Norrie's disease. *J Med Genet* 1979;**16**:125–8.

[12] Parving A, Warburg M. Audiological findings in Norrie's disease. *Audiology* 1977;**16**:124–31.

[13] Blodi FC, Hunter WS. Norrie's disease in North America. *Doc Ophthalmol* 1969;**26**:434–50.

[14] Warburg M. Norrie's disease. *J Ment Defic Res* 1968;**12**:247–51.

[15] Reynell J. *Manual for the Reynell-Zinkin scales.* London: National Foundation of Education Research, 1979.

[16] Elliott CD, Murray DJ, Pearson LS. *British ability scales.* Windsor: National Foundation of Educational Research-Nelson, 1978.

[17] Warburg M. Norrie's disease – differential diagnosis and treatment. *Acta Ophthalmol (Copenh)* 1975;**53**:217–36.

[18] Sonksen PM. Vision and early development. In: Wybar K, Taylor D, eds. *Pediatric ophthalmology.* New York: Marcel Dekker, 1983:85–95.

[19] Harendra de Silva DG, De Silva DBK. Norrie's disease in an Asian family. *Br J Ophthalmol* 1988;**72**:62–4.

[20] Sonksen PM. Constraints upon parenting: experience of a paediatrician. *Child Care Health Dev* 1989;**15**:No 1.

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Chronic cough in a hospital population; its relationship to atopy and defects in host defence

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SUMMARY The background and aetiology of chronic cough were investigated by comparing 60 children under 6 years with simple cough, 60 children with asthma, and 60 controls. Both cough and asthma were more common in boys and associated with a history of eczema, chest deformity, and skin reactivity to inhaled allergens, but these findings were more prevalent in asthma than cough. House dust mite sensitivity was found in 34 (57%) children with cough, 45 (75%) with asthma, and six (10%) controls. Tests of immunological function showed some high concentrations of IgM in groups with both cough and asthma, but high IgE concentrations, eosinophilia, and lymphocytosis were significant only in asthma. IgG_1 and IgG_2 concentrations were raised in some children with cough or asthma, but the only low subclass concentrations were of IgG_3 observed in the group with cough. Children with simple cough represented a heterogeneous population but many showed evidence of atopy. Major defects of immunity were not observed.

Cough is a symptom of respiratory disease but is not an illness in itself. The most common cause is a self limiting viral infection of the upper respiratory tract which lasts from a few days to two to three weeks.[1] A persistent or recurrent cough in a young child is a familiar problem in paediatric practice but it can be difficult to determine the aetiology. There may be an identifiable chronic infection, for example, pertussis or tuberculosis, a source of recurrent infections, for example, cystic fibrosis or bronchiectasis, or a history suggesting aspiration. Cough associated with wheeze and dyspnoea generally indicates asthma.[2-4] In many cases the coughing child suffers from no recognisable disease but complains of a non-productive cough without wheeze that interrupts sleep, disturbs the family and may restrict activity. The cough is frequently resistant to innumerable remedies, which include cough suppressants, decongestants, antibiotics, and inhalations.

Chronic persistent cough has been attributed to ill defined conditions that reflect current opinions rather than medical evidence. The literature cites 'post-nasal drip', enlarged adenoids, 'sinobronchitis', 'chronic bronchitis of childhood', and more recently gastro-oesophageal reflux or recurrent upper respiratory tract infection with impaired immunity.[5-12] The current trend is to attribute chronic cough to mild or early asthma precipitated by house dust, exercise, or frequent viral infections of the upper respiratory tract. Parents of asthmatic children often recall frequent episodes of cough before the child develops wheeze, and impaired lung function or increased bronchial reactivity have been reported in older children and adults with chronic cough.[13-17] Exercise or nocturnal cough may be attributed to asthma but there is little direct evidence that cough alone indicates asthma in children too young to cooperate with lung function tests.

This study identifies 60 children under 6 years old with chronic simple cough and compares their medical history, physical findings, immunological indices and skin reactivity to inhaled allergens with 60 children with asthma and 60 children without respiratory symptoms. The purpose was to determine whether children with cough could be distinguished from those with asthma or from children without respiratory symptoms with regard to evidence of atopy or defects in humoral immunity that could predispose to upper respiratory tract infection.

Patients and methods

In the cough group 60 children up to 6 years of age were recruited. They comprised all children referred to a paediatric outpatient clinic with persistent cough (lasting more than two months) or frequent episodes of cough—that is, cough for one week each month during the previous six months. The cough was not associated with audible wheeze and medical advisors had heard no added sounds on ausculation of the chest. Three of the 60 children had been referred initially to the ear, nose, and throat department but cough was their predominant symptom.

In the asthma group 60 children attending outpatients were studied. They were children in whom asthma was defined as cough with wheeze, breathlessness, and bronchospasm during at least two separate episodes over a period exceeding two months. None was taking oral steroids.

Children with abnormal chest radiography (other than hyperinflation and mild bronchial thickening), evidence of systemic disease, and with ill defined wheeze or bronchospasm were excluded from both the cough and asthma groups.

The control group comprised 60 children of similar age recruited from hospitals in the area. They were admitted for routine surgical procedures: circumcision (n=25), hernia (n=15), orchidopexy (n=5), strabismus (n=4), and minor urological procedures (n=8); three were outpatients attending for medical conditions other than those involving the chest (encopresis, enuresis, and feeding problems). Children with a history of frequent respiratory infections and those admitted for ear, nose, and throat surgery were excluded.

The children in the cough and asthma groups were recruited consecutively but the inclusion of control patients was adjusted to obtain a similar sex ratio to those in the cough and asthma groups. Informed verbal consent was obtained from a parent. The study was approved by the ethical committees of each district health authority.

The children in the cough and asthma groups were examined by the consultant paediatrician (HML) who completed a standard proforma, assisted by the research sister (HT). The research sister herself interviewed the parents of control children and completed the questionnaire with the help of the admitting surgical house officer. All children in the study (180) were weighed and measured and the measurements were plotted on centile charts.[18]

Children underwent skin prick tests with eight common inhalent allergen extracts using Merck reagents: house dust mite (*Dermatophagoides pteronyssinus*), house dust, cat fur, dog fur, grass pollen, tree pollen, mixed feathers, mixed moulds and with histamine and a control solution. All tests were performed by the research sister. A wheal diameter 3 mm greater than any control wheal was regarded as positive.

Five ml of blood was taken for: differential white cell count, total serum immunoglobulins, immunoglobulin G subclasses, classical and alternative complement pathway activity, and opsonisation capacity. Whole blood was transported to the immunology laboratory within two hours where serum was separated and stored at −70°C.

LABORATORY METHODS

Full blood counts were measured on a Coulter S and a manual differential count estimated on 100 cells. Serum immunoglobins and complement components C3 and C4 were measured by rate nephelometry (Beckman Auto ICS). Classical complement pathway activity (CH_{50}) was measured by Mayer's method[19] and alternative pathway activity by a modification of the method of Platts-Mills and Ishizaka.[20] Immunoglobulin G subclasses (G_1–G_4) were measured by single radial immunodiffusion using suitable mouse monoclonal antibodies assigned by an International Union of Immunological Societies/WHO Study (Binding Site Ltd).[21] The standard used was the UK SPSO1 calibrant (SAS Protein Reference Unit). The sensitivity of the assay ranged from 0·1 g/l for IgG_1 to 0·05 g/l for IgG_4.

Results were accepted only if the sum of the four IgG subclasses was within 10% of the total IgG measured by rate nephelometry. Total IgE was measured by an immunoradiometric assay (Hybritech Tandem R IgE) and opsonisation of saccharomyces cerevisiae by the method of Yamamura, Bolder, and Valdimarsson and expressed as a percentage of a normal human reference serum aliquoted and stored at −70°C.[22]

STATISTICAL METHODS

Data from cough, asthma, and control groups were presented on three by two contingency tables and analysed using χ_2^2 (two degrees of freedom), and when results indicated deviation from a null hypothesis ($\chi_2^2<0·05$) each of the three groups was retested against each other using χ_1^2 (one degree of freedom), with Yates's correction.

The immunological data were tested for a normal distribution using a Kolmogorov-Smirnov test for goodness of fit. Data analysis was based on nonparametric methods because of the skewed distribution of most of the immunological parameters. Mann-Whitney U tests and Kruskal-Wallis one way analysis of variance were used to compare values between the three groups. The effects of age on the data were examined visually by scatter plots and by using Spearman rank correlation coefficients.

Table 1 *Sex and age distribution and medical and social history of children in study*

	Cough (n=60)	*Asthma (n=60)*	*Control (n=60)*	*Significance*
No of boys (%)	44 (73)	42 (70)	45 (75)	
No of girls (%)	16 (27)	18 (30)	15 (25)	
Median age (years)	3·4	2·7	4·2	*
Age range (years)	0·5–5·9	0·5–6·2	0·5–6·4	
No (%) with history of eczema	16 (27)	27 (45)	7 (12)	*
No (%) with possible whooping cough in previous year	6 (10)	0	8 (13)	*
No (%) with duration of respiratory symptoms >1 year	21 (35)	35 (58)	0	*
No (%) with asthma in parent or sibling	20 (33)	23 (38)	13 (22)	
No (%) with smoker in household	33 (55)	33 (55)	25 (42)	
No (%) with single or unemployed parent	15 (25)	13 (22)	9 (15)	

*=p<0·05 by χ^2_2.

Results

SEX AND AGE DISTRIBUTION AND MEDICAL AND SOCIAL HISTORY (TABLE I)

There were more boys than girls in both cough and asthma groups. Controls were significantly older than other children in the study (Kruskal-Wallis analysis of variance: F=7·33, p=0·001) but this was considered in the statistical analysis. There was a significant increase in a history of eczema in those with asthma compared with controls (χ^2_1=14·8, p=0·0003). Eczema was reported less often with cough than with asthma (χ^2_1=3·62, p=0·05) but more often than in the control group (χ^2_1=3·44, p=0·06). No child with asthma gave a history of possible whooping cough in the previous 12 months (χ^2_2=8·06, p=0·018) but the diagnosis might not be suspected in an asthmatic. In none of the children with cough had pertussis been proved bacteriologically. More children with asthma gave a history of respiratory symptoms exceeding one year than those with simple cough (χ^2_1=5·66, p=0·017). In the cough and asthma groups there were more children with a family history of asthma, with a smoker in the household, or with an unemployed or single parent, but these findings were prevalent in control families and failed to reach significance.

There were no significant differences between the three groups in the frequency of neonatal respiratory illness, in a history of pneumonia or bronchiolitis in the first year, or of urticarial reactions. Neither the racial origin of the parents nor perception of damp housing could be related to cough or asthma.

PHYSICAL EXAMINATION

The centiles for height and weight were plotted as a histogram for each group and showed a similar distribution in each. Chest deformity (troughing of the rib cage or sternal bowing) was considered mild or marked in 10/60 (17%) in children with cough, 27/60 (45%) with asthma, and in none of the controls. Chest deformity was observed in significantly more children in the asthma than in the cough group (χ^2_1=8·84, p=0·003).

INVESTIGATIONS

Skin tests

Significantly more children with asthma or cough reacted positively to skin testing than controls (χ^2_2=63·3, p<0·0001) and the frequency of reactions was higher in asthma than cough (χ^2_1=4·03, p=0·04). Reaction to house dust mite was the single most common sensitivity (table 2).

Table 2 *Skin test reactions to inhaled allergens*

	Cough (n=60)	*Asthma (n=60)*	*Control (n=60)*	*Significance*
No (%) with one or more positive results†	38 (63)	48 (80)	6 (10)	*
No (%) positive to house dust mite	34 (57)	45 (75)	6 (10)	*
No (%) with five or more positive reactions	15 (25)	24 (40)	0	*

*=p<0·05 by χ^2_2.
†Wheal >3 mm.

Differential white cell counts

Peripheral white cell counts were analysed in 56 children with cough, 58 with asthma, and in 60 controls. A moderate rise of the lymphocyte count (5·0–10·0×10^9/l) was observed in 29 children with asthma compared with 13 with cough and seven controls (χ^2=21·17 p=0·0001) but a count exceeding 10·0×10^9/l was found in only two children, both in the cough group. A moderate rise of the eosinophil count (0·5–1·0×10^9/l) was observed in 15 children with asthma, five with cough, and in three controls (χ^2=12·51 p=0·002). Eosinophil counts exceeding 1·0×10^9/l were recorded in only five children with asthma, four with cough, and in one control; this was not significant.

Alternative complement pathway

There was no significant difference in alternative pathway activity between the three groups and no dependence on age. Activity was low in 3/60 children with cough, 7/60 with asthma, and in 6/60 controls.

Immunoglobin and IgG subclass concentrations and classical complement pathway (60 children in each group)

Only IgG and IgM concentrations (for entire population and each group) were consistent with a normal distribution, so suitable non-parametric tests were used in preference to log transformation.[23] All serum concentrations except IgM and IgG were highly correlated with age when the whole population was examined (Spearman rank correlation coefficient, p<0·05). Scatterplots of age against concentration were examined visually and a plateau at 3 years was apparent. Each group was then divided into those under 3 years and those 3 years old or more. When the correlation coefficients were recalculated for children aged 3 years and over the effect of age was not significant for all indices except IgA and IgE concentrations, which continued to rise; hence only those over 3 years were included in the comparative analysis.

Table 3 *Fifth and 95th centile and median values for immunology in 46 control children aged 3–6 years*

	5th Centile	*Median*	*95th Centile*
IgG (g/l)	<4·45	7·5	>10·9
IgA (g/l)	<0·34	0·66	>1·12
IgM (g/l)	<0·12	0·81	>1·29
IgE (kU/l)	<1·0	16·3	>540
IgG_1 (g/l)	<3·25	5·22	>7·4
IgG_2 (g/l)	<0·37	0·99	>2·07
IgG_3 (g/l)	<0·18	0·33	>0·51
IgG_4 (g/l)	<0·02	0·2	>0·84
CH_{50} (U/10^3/l)	<24	36	>47
C3 (g/l)	<0·65	0·92	>1·28
C4 (g/l)	<0·10	0·15	>0·22
Opsonisation capacity*	<73	101·5	>110

*%Laboratory control.

In the age range 3–6·4 years there were 36 children with cough, 28 with asthma, and 46 controls. For all the immunological indices the median, fifth, and 95th centile values were calculated from the control group in order to establish the population's normal range (table 3). The cough and asthma groups had significantly higher concentrations of IgM than the control group (Mann-Whitney U test, p=0·02).

The IgE levels in the asthma group were much higher than in cough or control groups. In all three groups IgE showed a distribution skewed towards high concentrations. Even in the control group 6/46 children had values of IgE above a generally accepted upper limit of 100 kU/l. Two of these children had reacted positively to skin testing but the other four had no evidence of atopy. There were no significant differences in the distribution of IgA and total IgG or IgG subclasses between the three groups, but there was a trend towards high IgG_1 concentrations in cough (p=0·06) and high IgG_2 concentrations in asthma (Mann-Whitney U test, p=0·09). In order to identify small subgroups of patients with immunological abnormalities contingency tables were drawn of those children with cough or asthma whose immunological indices fell outside the fifth to 95th centile range established from the control, group (table 4). High IgG_1 and

Table 4 *Immunological abnormalities in children with asthma and cough, outside the fifth and 95th centile range for controls aged 3–6 years. Results are No (%)*

	Cough (n=36)	*Asthma (n=28)*	*Control (n=46)*	*Significance (χ^2_2, p value)*
High IgM	11 (31)	8 (29)	4 (9)	7·17, 0·027
High IgE	0	8 (29)	3 (7)	15·35, 0·0008
High IgG_1	11 (31)	5 (18)	3 (7)	8·17, 0·017
High IgG_2	0	5 (18)	3 (7)	7·51, 0·023
Low IgG_3	11 (31)	2 (7)	1 (2)	15·7, 0·0007

IgG_2 concentrations were apparent in cough and asthma. Low concentrations of IgG subclasses were observed only for IgG_3 and in children with cough but the values were only just below the 5th centile control level, hence this effect was not shown using the Mann-Whitney U test. There were no significant differences between the three groups for C3 or C4 concentrations, CH_{50}, or opsonisation capacity using either the Mann-Whitney U test or contingency tables. An abnormality of more than one immunological variable was observed in a few children but the numbers were too small to establish interrelationship. Similarly no correlation could be shown between immunological data and positive skin tests.

Discussion

Most children with chronic simple cough showed evidence of atopy in their reactions to skin testing and their history of eczema. Cough and asthma were both more common in boys; a male:female ratio exceeding 2·0:1 is comparable with the male preponderance of childhood asthma reported in most western countries and attributed in part to the greater susceptibility of boys to respiratory infections.[24 25]

This study has not proved that cough in children with atopy but no wheeze is equivalent to cough in asthma. The observation of chest deformity in some children with cough implied chronic airway obstruction but they had no other clinical evidence of bronchoconstriction, and they were too young to cooperate with tests of bronchial reactivity. The cough could be due to IgE mediated hypersensitivity to house dust mite with inflammatory reaction and stimulation of cough receptors in the respiratory tract but little or no bronchoconstriction and therefore no wheeze or breathlessness.

Previous studies have described 'cough variant asthma' but in older children able to perform lung function tests or in younger children who showed a subjective response to bronchodilators.[13-17] Only in the present study have the features of simple cough been compared with typical asthma or with healthy controls.

There were no features of atopy in about 40% of children in the cough group. Persistent cough for more than two months excluded most viral infections or pertussis but isolation of micro-organisms was not part of the protocol. Environmental effects—for example, passive smoking and damp housing—might be relevant if measured objectively.[26] Other factors that could be considered to provoke cough include psychogenic cough[27] (rarely found below 6 years of age) or inhalation from gastro-oesophageal reflux at night.[1 3] Oesophageal pH measurements were not undertaken but none of the children had clinical or radiographic features suggestive of inhalation.

There was no evidence that children with cough or asthma suffered severe deficiencies of immunoglobulins or of IgG subclasses that have recently been associated with both atopy and recurrent upper respiratory tract infections.[12 28-30] Slightly low concentrations of IgG_3 were found in 31% of children with cough but many (cough and asthma) showed a rise of immunoglobulins indicative of a stressed but not inadequate immunological system. Below the age of 3 years immunoglobulin values were strongly dependent on age and it was not possible to establish a normal range from the small numbers in the control group. In a much larger population of healthy children, Isaacs *et al* reached a similar conclusion and warned against making a diagnosis of partial immunoglobulin deficiency from a single sample.[23] Defects in complement function and opsonising capacity have been described in children and adults with cough or recurrent respiratory infections,[11 31] but in the present investigation low values were no more frequent than in healthy controls.

There could be some bias in the comparison of immunological data as the controls were from a hospital population of children who were, by selection, free from intercurrent or recurrent infection, unlike a random population sample.

The immunological protocol did not include measurement of salivary IgA, functional antibody response to immunisation, cell mediated immunity, neutrophil function or interferon production. Abnormalities of all these variables have been reported in association with frequent infections and with atopy.[8-10 28 32]

This review has shown many similarities between simple cough and asthma, most obviously sensitivity to house dust mite. A prospective study of the cohort of the 60 children with cough is in progress in order to explore precipitating factors and determine whether chronic cough is a minor self limiting symptom or one which heralds the onset of classical asthma.

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References

[1] Cloutier MM. The coughing child. *Postgrad Med* 1983;**73:** 169-75.

[2] Eigen H. The clinical evaluation of chronic cough. *Pediatr Clin North Am* 1982;**29:**67-78.

[3] Mellis CM. Evaluation and treatment of chronic cough in children. *Pediatr Clin North Am* 1979;**26:**553–64.

[4] Williams HE. Chronic and recurrent cough. *Aust Paediatr J* 1975;**11:**1–8.

[5] Phelan PD. Post-nasal drip and chronic cough. *Lancet* 1978;**ii:** 1309.

[6] Smith C. Night cough in children. *Lancet* 1979;**i:**732.

[7] Stell PM, Pahor AL. Night cough in children. *Lancet* 1979;**i:**616.

[8] Isaacs D, Webster ADB, Valman HB. Immunoglobulin levels and function in pre-school children with recurrent respiratory infections. *Clin Exp Immunol* 1984; **58:** 335–40.

[9] Isaacs D, Clarke JR, Tyrrell DAJ, Valman HB. Selective infection of lower respiratory tract by respiratory viruses in children with recurrent respiratory tract infections. *Br Med J* 1982;**284:**1746–8.

[10] Beard LJ, Maxwell GH, Thong YH. Immunocompetence of children with frequent respiratory infections. *Arch Dis Child* 1981;**56:**101–6.

[11] Richardson VF, Larcher VF, Price JF. A common congenital immunodeficiency predisposing to infection and atopy in infancy. *Arch Dis Child* 1983;**58:**799–802.

[12] Morgan C, Levinsky RJ. Clinical significance of IgG subclass deficiency. *Arch Dis Child* 1988;**63:**771–3.

[13] Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperactivity. *Pediatrics* 1981;**67:**6–12.

[14] Ellul-Micallef R. Effect of terbutaline in chronic 'allergic' cough. *Br Med J* 1983;**287:**940–3.

[15] Hannaway PJ, Hopper DK. Cough variant asthma in childhood. *JAMA* 1982;**247:**206–8.

[16] Konig P. Hidden asthma in childhood. *Am J Dis Child* 1981;**135:**1053–5.

[17] Spelman R. Chronic or recurrent cough in children: a presentation of asthma? *J R Coll Gen Pract* 1984;**34:**221–2.

[18] Tanner JM, Whitehouse RM, Takaishi M. Standards from birth to maturity for height, weight. height velocity and weight velocity. British children 1965. Part 1. *Arch Dis Child* 1966;**41:** 454–71.

[19] Mayer MM. Complement and complement fixation. In: Kabat EA, Mayer MM, eds. *Experimental immunochemistry*. 2nd ed. Springfield, Ohio: Thomas, 1961:133.

[20] Platts-Mills TAE, Ishizaka K. Activation of the alternative pathway of human complement by rabbit cells. *J Immunol* 1974;**113:**348.

[21] Jefferis R, Reimer CB, Skvaril F, *et al.* Evaluation of monoclonal antibodies having specificity for human IgG subclasses: results of an IUIS/WHO collaborate study. *Immunol Lett* 1985;**10:**233–52.

[22] Yamamura M, Bolder J, Valdimarsson H. Phagocytosis measured as inhibition of uridine uptake by candida albicans. *J Immunol Methods* 1977;**14:**19.

[23] Isaacs D, Altman DG, Tidmarsh CE, Valman HB, Webster ADB. Serum immunoglobulin concentrations in preschool children measured by laser nephelometry: references ranges for IgG, IgA and IgM. *J Clin Pathol* 1983;**36:**1193–6.

[24] Gregg I. Epidemiological aspects. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall, 1983:242–84.

[25] Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;**286:**1256–8.

[26] Martin CJ, Platt SD, Hunt SM. Housing conditions and ill health. *Br Med J* 1987;**294:**1125–7.

[27] Milner AD. Psychogenic cough in childhood. *Br Med J* 1985;**290:**1847–8.

[28] French MAH, Harrison G. Systemic antibody deficiency in patients without serum immunoglobulin deficiency or with selective IgA deficiency. *Clin Exp Immunol* 1984;**56:**18–22.

[29] Smith TF, Bain RP. IgG subclasses in children with chronic chest symptoms. *Monogr Allergy* 1986;**20:**119–27.

[30] Loftus BC, Price JF, Lobo-Yeo A, *et al.* IgG subclass deficiency in asthma. *Arch Dis Child* 1988;**63:**1434–7.

[31] Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. *Medicine (Baltimore)* **63:**243–73.

[32] Isaacs D, Clarke JR, Tyrrell DAJ, Webster ADB, Valman HB. Deficient production of leucocyte interferon (interferon-α) in vitro and in vivo in children with recurrent respiratory tract infections. *Lancet* 1981;**ii:**950–2.

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Pseudomonas aeruginosa antibodies in blood spots from patients with cystic fibrosis

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SUMMARY The formation of antibodies to *Pseudomonas aeruginosa* may be the earliest indicator of pulmonary infection in patients with cystic fibrosis. To enable easy sampling in babies and young children an enzyme linked immunosorbent assay (ELISA) based on a blood spot sample taken on to blotting paper was developed. A sample of approximately 20 µl of blood was required. A high correlation and level of absolute agreement was shown between paired finger prick and venepuncture blood spots, and between blood spot, serum spot, and serum samples. Healthy controls and non-infected patients with cystic fibrosis had low titres of antibody compared with patients with intermittent and chronic infection. The latter groups had significantly greater antibody titres than normal controls. This assay permits serial measurement of antibodies to *P aeruginosa* in patients of all ages with cystic fibrosis and may provide a means of assessing the value of such measurements in the detection and management of early infection.

Chronic lung infection with *Pseudomonas aeruginosa* is the main cause of morbidity and mortality in patients with cystic fibrosis.[1] There may be a period of harmless colonisation of the respiratory tract before infection becomes chronic, after which the organism is never completely eradicated from the lungs. Lung injury caused by chronic infection is probably mediated by the formation of immune complexes between *P aeruginosa* derived antigens and host immunoglobulins.[2 3]

Chronic *P aeruginosa* infection may be diagnosed by the determination of specific IgG class antibodies in serum by counterimmunoelectrophoresis or enzyme linked immunosorbent assay (ELISA).[4-6] A specific antibody response may be detected before there is regular isolation of the organism from sputum.[5 6] This early host response may also indicate the presence of lung injury,[2 3] but it is not clear how knowledge of an increased antibody titre should be used in the management of patients in the early stages of *P aeruginosa* infection.

The acquisition of *P aeruginosa* occurs at an early age and it is in children that the application of antibody measurements may have the greatest potential for diagnosis and early treatment to protect the lungs. Serial determination of serum antibodies in young children is, however, difficult in practice and may be unacceptable to patients and parents. To overcome this an ELISA for IgG antibody to *P aeruginosa* carried out on blood spot specimens from finger prick samples was developed.

Subjects and methods

Paired blood spot and serum samples were obtained by venepuncture from patients attending adult and paediatric cystic fibrosis clinics. Blood spot samples were also collected by finger prick. Data from the latter collection method are specifically indicated in the text. Adult patients with bronchiectasis and *P aeruginosa* infection also had samples taken. These studies were approved by the local ethics committee. Controls were drawn from healthy hospital workers and their families, and from children having blood taken for other reasons.

PROCESSING OF SPECIMENS

Serum was stored at −70°C until assay. Blood spots were collected onto Guthrie cards and stored in sealed plastic envelopes at −20°C. To control for the effect of the blotting paper and blood cells, spots were also made with freshly separated serum and dealt with in the same manner as the blood spots. The centre of each serum or blood spot was punched out using a standard 6 mm diameter paper punch. Each disc contained approximately 10 µl of whole blood or 8 µl serum (the serum dispersed over a larger area on the Guthrie cards) and was handled with forceps. The discs were incubated in 300 µl of phosphate buffered saline (pH 7·4) for one hour at 37°C to elute antibody. The discs were removed and the eluate diluted 1:20 with phosphate buffered saline before assay.

ELISA

A direct antibody capture ELISA was developed using soluble antigens prepared from *P aeruginosa* serotypes 01–17.[7] The protein concentration of this preparation was 22 g/l. Flat bottomed, 96 well, cobalt irradiated, microtitre plates (Immulon 2, Dynatec) were coated with antigen in phosphate buffered saline, pH 7·4 (100 µl/well, 1·1 µg protein) for one hour. Excess antigen was removed by inversion of the plate and two washes with phosphate buffered saline. Blocking was performed with freshly prepared 0·05% gelatin solution in phosphate buffered saline (100 µl/well) for one hour. Plates were then washed four times with phosphate buffered saline 0·01% Tween 20 (BDH) buffer. The first wash was a rapid one and the subsequent three entailed a four minute soak before emptying. Diluted serum (1:2000 in phosphate buffered saline) or eluate (50 µl/well) was added and incubated for one hour. Plates were then washed four times as before. Biotinylated goat antihuman IgG (γ chain specific, Sigma Chemical Co) diluted 1:1000 with phosphate buffered saline was added (50 µl/well) and incubated for 60 minutes. Plates were washed four times as before. Avidin peroxidase conjugate (ICN Immunobiological Ltd) diluted 1:1000 in borate saline buffer pH 8·6 (50 µl/well) was added and incubated for one hour. Wells were washed as before with a borate saline, 0·01% Tween 20 buffer (pH 8·6). The peroxidase substrate mixture was freshly prepared (1 mg/ml 5-amino salicylic acid, in 0·02M phosphate buffer pH 6·8, was pretreated with 1–5 mg of activated charcoal/100 ml and filtered before use, when 1 ml/100 ml of freshly prepared 1% (v/v) hydrogen peroxide was added). This solution (100 µl/well) was allowed to act for 30 minutes before 50 µl of 3M sodium hydroxide was added to stop the reaction. Absorbance was read within five minutes of stopping the reaction in an automatic microtitre plate recorder (Kontron Ltd) at a wavelength of 455·5 nm. Assays were performed at room temperature with continuous gentle mixing.

STANDARDISATION OF ELISA DATA AND STATISTICAL METHODS

A high titre serum from a patient with chronic pseudomonal infection, and a pool of normal low titre serum samples, were used as references. Non-specific binding was reduced by using a high dilution and was controlled for by the inclusion of eight wells with no antigen on each plate. An ELISA index was derived as follows (OD, optical density):

$$\frac{\text{Unknown OD}-\text{low control OD}}{\text{High control OD}-\text{low control OD}}\times 100$$

Low control OD is the absorbance of the low titre serum in no antigen wells, high control OD is the absorbance of the high titre control serum, and unknown OD is the absorbance of the specimen being assayed.[8] Intra-assay and interassay variation were monitored with two whole blood spot samples assayed in eight replicates/assay.

Normally distributed data were expressed as mean and standard deviation or coefficient of variation (standard deviation/mean). Significance of differences were assessed by a Student's *t* test. The relationships between sampling methods were compared by linear regression and a method of agreement.[9] Non-normally distributed data were expressed as medians and ranges. The significance of differences between groups were determined with the Mann-Whitney U test.

Results

PERFORMANCE CHARACTERISTICS OF THE ASSAY

Using two control serum samples, the mean intra-assay variation (expressed as coefficient of variation) was 7·6% (range 1·6–14·2) and 6·6% (range 1·8–12·7) in seven consecutive assays. For the same seven assays these controls gave a mean (SD) of 83 (4·1) and 74·1 (4·3) ELISA index units, giving interassay variations of 8·7 and 8·5, respectively.

COMPARISON OF SERUM WITH BLOOD SPOT, SERUM SPOT, AND FINGER PRICK SPECIMENS

Paired serum and blood spot specimens were significantly related (n=108, p<0·001 (fig 1). There was a significant relationship between serum spot specimens and both serum and blood spot specimens, p<0·001 and p<0·001, respectively (n=87). The agreement between the different specimens was assessed by the determination of the mean difference (95% confidence interval) for paired specimens. For blood spot specimens compared with serum specimens (n=108) the mean difference was 2·7 (1·6 to 3·7) ELISA index units, and for the blood spot specimens compared with serum spot specimens (n=87) the mean difference was 0·05 (−0·9 to 1·8).

Finger prick sample results were closely related to those of paired blood spot and serum samples. Determination of agreement showed that the finger-prick blood spot specimens tended to give slightly lower results than paired blood spot and serum samples (n=23), the mean difference being −1·6

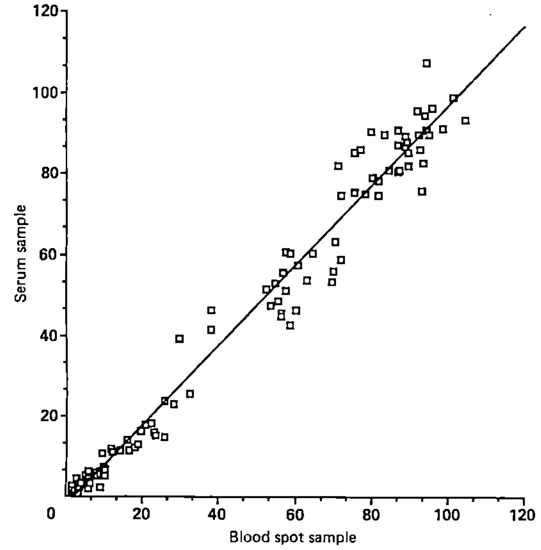

Fig 1 *Relationship between paired blood spot samples and routine serum samples from venous blood. The plot is of 108 paired samples from normal subjects and bronchiectatic patients with and without cystic fibrosis. The least squares regression line is shown. The results are expressed as ELISA index units.*

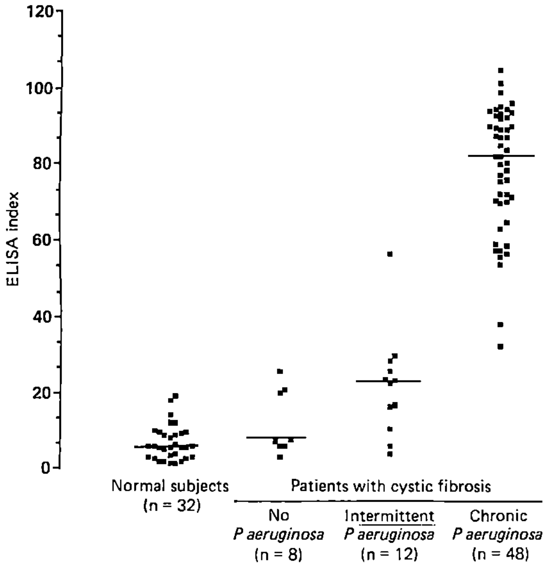

Fig 2 *ELISA index results for normal subjects and patients with cystic fibrosis according to the isolation pattern for P aeruginosa. Blood spots were made from venous blood. Individual results are shown with the median for each group.*

(−4·0 to 0·9) and −1·5 (−3·6 to 0·7) ELISA index units, respectively.

EFFECT OF BLOOD SPOT VOLUME

This was assessed by making blood spots with 10, 20, 30, and 50 μl volumes of whole blood from a single patient; 10 μl was the minimum volume from which a 6 mm disc could be reliably punched. There were no significant differences between discs, indicating that the blood volume had little effect on antibody determination (analysis of variance, F=1·232; 3, 30 df, p=0·315).

STORAGE OF BLOOD SPOT SPECIMENS

Paired blood spots were prepared from 28 patients. One sample was assayed freshly and a second blood spot specimen was stored at −20°C for 21 to 28 days before eluates were prepared. An assessment of agreement revealed a mean difference of 1·5 ELISA index units with a 95% confidence interval of −1·7 to 4·7.

COMPARISON OF PATIENTS WITH CYSTIC FIBROSIS WITH AND WITHOUT *P AERUGINOSA* INFECTION

There was no significant difference between patients with cystic fibrosis in whom *P aeruginosa* had never been isolated from the sputum and healthy controls not known to have been infected at any time (fig 2). Patients with either intermittent isolation of *P aeruginosa* (less than four isolates in one year) or chronic infection four or more isolations in one year) had significantly greater ELISA indices than controls (p<0·0002). There was overlap, however, between the former group and both the control group and the group with cystic fibrosis who had never been infected.

Discussion

The collection of small volumes of blood on blotting paper is used in screening babies for phenylketonuria[10] and neonatal hypothyroidism.[11–13] The same simple procedure was successful for the measurement of antibodies of the IgG class in this study and gave absolute values close to those obtained with serum samples.

The blood spot system is dependent on a reliable and reproducible assay. Reported ELISAs for pseudomonas antibodies did not have the within and between assay performances of the highly developed method used here. Using the same antigen as in this study a similar ELISA gave intraplate, intra-assay, and interassay variations of 14%, 19%, and 20%, respectively.[5] The assay reported here could be completed in one working day, whereas other reported assays require one or two overnight incubation periods.[4 5] Blood spot samples could be stored at −20°C for up to four weeks without deterioration, which suggests that such samples may be stored for long periods in such conditions. This is supported by the stability of such specimens after being stored for up to nine months at −20°C, which was as good as for paired serum specimens in storage.[14] Another possibility yet to be studied is that blood spot specimens will keep for short periods, in a dry form at ambient temperatures, allowing them to be taken at home and posted to the laboratory for assay. This would be an advantage in epidemiological studies or for serial monitoring.

In the assay reported here normal subjects had low but detectable antibody titres, which probably indicates a general low degree of response in normal subjects.[15] This group was not statistically different from patients with cystic fibrosis who had never grown *P aeruginosa* from their sputum. The patients with cystic fibrosis and intermittent growth of *P aeruginosa* were separated from normal controls but overlapped with both the non-infected patients with cystic fibrosis and those with chronic infection, which suggests a range of exposure and host response to *P aeruginosa*. These findings confirm earlier reports and indicate the validity of the blood spot ELISA system reported here.[5 16 17]

It is not clear how to use data about antipseudomonal antibodies in the management of early infection. It is thought that intermittent isolation of *P aeruginosa* occurs during a phase of harmless colonisation, and that treatment during this period may delay or halt progression to chronic infection. Vigorous antipseudomonal antibiotic treatment does protect the lungs against injury and prolongs survival in chronically infected subjects,[18] but it is unknown if early intervention would have the same effect. The harmlessness of early colonisation is an assumption that could be tested by combining the method reported here with an index of lung destruction, such as measurement of urinary desmosine concentration.[19] Such an approach would help to define the role of antibody measurements in cystic fibrosis and the value of intervention with antibiotics early in *P aeruginosa* infection. In previous studies serial sampling has only been carried out in small numbers of patients at infrequent intervals, or simply to illustrate the value of an individual ELISA.[5 16 17]

Antibodies of the IgG class to *P aeruginosa* can reliably be determined using finger prick samples of blood collected on to Guthrie cards. This method of collection had a high level of agreement with blood samples obtained by venepuncture, which allows the prospect of repeated sampling in babies and children with cystic fibrosis with minimum disturbance to the child or parent. Such studies may define the association of antipseudomonal antibodies and the acquisition of infection, and the value of their determination in the management of early *P aeruginosa* infection in children with cystic fibrosis.

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References

1 Pier GB. Pulmonary disease associated with Pseudomonas aeruginosa in cystic fibrosis: current status of the host-bacterium interaction. *J Infect Dis* 1985;**151**:575–80.

2 Høiby N, Doring G, Schiotz PO. The role of immune complexes in the pathogenesis of bacterial infections. *Annual Review of Microbiology* 1986;**40**:29–53.

3 Dasgupta MK, Zuberbuhler P, Abbi A, *et al.* Combined evaluation of circulating immune complexes and antibodies to Pseudomonas aeruginosa as an immunologic profile in relation to pulmonary function in cystic fibrosis. *J Clin Immunol* 1987;**7**:51–8.

4 Høiby N. Antibodies against Pseudomonas aeruginosa in sera from normal persons and from patients colonised with mucoid or non-mucoid Pseudomonas aeruginosa. Results obtained by means of crossed immunoelectrophoresis. *Acta Pathologica et Microbiologica Scandinavian Section C: Immunology* 1977;**85**: 142–8.

5 Brett MM, Ghoneim ATM, Littlewood JM, Losowsky MS. Development of enzyme linked immunosorbent assay (ELISA) to detect antibodies to Pseudomonas aeruginosa cell surface antigens in sera of patients with cystic fibrosis. *J Clin Pathol* 1986;**39**:1124–9.

6 Pedersen SS, Espersen F, Høiby N. Diagnosis of chronic pseudomonas aeruginosa infection in cystic fibrosis by enzyme linked immunosorbent assay. *J Clin Microbiol* 1987;**25**:1830–6.

7 Høiby N. Pseudomonas aeruginosa infection in cystic fibrosis. Diagnostic and prognostic significance on Pseudomonas aeruginosa precipitins determined by means of crossed immunoelectrophoresis. A survey. *Acta Pathologica et Microbiologica Scandinavica, section C Immunology* 1977;**262**:(suppl):3–96.

8 Shale DJ, Faux JA. The evaluation of a quantitative enzyme-linked immunosorbent assay (ELISA) for anti-A fumigatus IgG. *J Immunol Methods* 1985;**77**:197–205.

9 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i**:307–10.

10 Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963;**32**:338–43.

11 Irie M, Enomoto K, Naruse H. Measurement of thyroid-stimulating hormone in dried blood spot. *Lancet* 1975;**ii**:1233–4.

12 Dussault JH, Parlow A, Letarte J, Guyda H, Laberge C. TSH measurements from blood spots on filter paper: a confirmatory screening test for neonatal hypothyroidism. *J Pediatr* 1976;**89**: 550–2.

13 Larsen PR, Merker A, Parlow AF. Immunoassay of human TSH using dried blood samples. *Journal of Clinical Endocrinology* 1976;**42**:987–90.

14 Guimaraes MCS, Castilho EA, Celeste BJ, Nakahara OS, Netto VM. Longterm storage of IgG and IgM on filter papers for use in parasitic disease seroepidemiology surveys. *Bull Pan Am Health Organ* 1985;**19**:16–28.

[15] Cost KM, West KS, Brinsen D, Polk HC. Measurement of human antibody activity against Escherichia coli and Pseudomonas aeruginosa using formal entreated whole organisms in an ELISA technique. *J Immunoassay* 1985;**6**:23–43.
[16] Brett MM, Ghoneim ATM, Littlewood JM. Serum antibodies to Pseudomonas aeruginosa in cystic fibrosis. *Arch Dis Child* 1986;**61**:1114–20.
[17] Brett MM, Ghoneim ATM, Littlewood JM. Serum IgG antibodies in patients with cystic fibrosis with early Pseudomonas aeruginosa infection. *Arch Dis Child* 1987;**62**:357–61.
[18] Pedersen SS, Jensen T, Høiby N, Koch C, Flensborg EW. Management of Pseudomonas aeruginosa lung infection in Danish cystic fibrosis patients. *Acta Paediatr Scand* 1987;**76**: 955–61.
[19] Bruce MC, Poncz L, Klinger JD, Stern RC, Tomashefski JF, Dearborn DG. Biochemical and pathological evidence for proteolytic destruction of lung connective tissue in cystic fibrosis. *Am Rev Respir Dis* 1985;**132**:529–35.

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Postpubertal gluten challenge in coeliac disease

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SUMMARY Altogether 38 postpubertal children with coeliac disease were rebiopsied. Mucosal abnormality in nine (24%) of them indicated poor adherence to the diet. Gluten challenge with a diet containing a normal amount of gluten was performed in those 29 patients with a normal mucosa. During challenge, rebiopsy was done when reticulin antibodies turned positive (mean 0·6 years, range 0·2–2·0) or at the end of the two year study. Histologically a clear relapse into coeliac disease was seen in all 23 patients who were positive for reticulin antibodies. At this time gliadin antibodies were positive in all but two. Sixteen (70%) of those who relapsed were completely asymptomatic. Three girls and one boy did not relapse within two years, indicating the possible recovery from coeliac disease to be 11%. All four had undergone gluten challenge earlier in childhood, after initial diagnosis and mucosal recovery, and this had resulted in mucosal relapse. To establish definite postpubertal recovery from coeliac disease in cases with normal mucosa at two years from challenge, further follow up studies of reticulin antibodies and later rebiopsy are needed. The reticulin antibody test seems to be suitable for prediction of mucosal relapse in coeliac disease.

The European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) criteria for diagnosing coeliac disease include, after initial diagnosis, prechallenge verification of normal small bowel mucosa and postchallenge mucosal relapse.[1 2] In Finland the clinical picture of coeliac disease has changed to milder forms, resulting in an upward shift of age at diagnosis.[3] In fact, over 60% of the diagnoses today are made at school age and during adolescence. The current problem is when to apply gluten challenge in children with late diagnosis. It has also been discussed whether routine gluten challenge should be performed at all, as only a few patients with coeliac disease will not relapse after gluten reintroduction.[4] On the other hand puberty could be a milestone in coeliac disease, after which the disease behaves differently. In fact, Schmitz *et al* have shown spontaneous remissions of coeliac disease during adolescence.[5] Therefore we felt it appropriate to reinvestigate children with coeliac disease postpubertally.

We have now performed postpubertal gluten challenge on adolescents and young adults in whom the diagnosis of coeliac disease was made both in infancy, including gluten challenge, and at a later age. The purpose of the study was to establish whether there are patients with coeliac disease already fulfilling the ESPGAN criteria and probable patients who do not relapse postpubertally within two years on a diet containing gluten. We also hypothesised that only one biopsy would be needed during gluten challenge, the appearance of reticulin antibodies during the challenge being the indicator for rebiopsy. At the same time gliadin antibodies were also measured.

Patients and methods

STUDY DESIGN

Altogether 42 adolescents and young adults were asked to join the study. They were informed as to the study programme, which included initial biopsy and gluten challenge by means of a diet containing a normal amount of gluten but with at least 10 g of gluten per day. Follow up visits were to be made first after one month and later every three months during the challenge or in the meantime if symptoms occurred. Blood samples for IgA and IgG class reticulin and gliadin antibodies were to be drawn at the follow up visits. The study also included rebiopsy at the time of appearance of reticulin antibodies or symptoms, with a deadline of two years of gluten challenge. The patients were told that they would most probably have to return to the gluten free diet after the study, but also that coeliac disease might disappear during adolescence as suggested by Schmitz *et al.*[5]

PATIENTS

A total of four patients refused to join the study and continued with a gluten free diet. Thirty eight patients underwent initial small bowel biopsy and nine (24%) of them were excluded from the study because of apparent poor adherence to the diet and the finding of mucosal changes compatible with coeliac disease (from slight partial villous atrophy to flat mucosa).

A diet containing a normal amount of gluten was reintroduced in 29 patients (13 boys and 16 girls). All had normal small bowel mucosa on biopsy and all were negative for reticulin antibodies. Mean age at commencement of the study was 16·6 years (range 14·3–22·1). ESPGAN criteria with an earlier gluten challenge had been fulfilled in 20 patients. The median age of these 20 patients at the initial diagnosis was 1·0 year (range 0·5–4·0). They had been on a gluten free diet before this second challenge for a mean of 8·5 years (range 3·0–13·0). The median age at the initial diagnosis of the nine patients undergoing their first gluten challenge was 10·0 years (range 1·0–15·3). The mean duration of gluten free diet was 7·8 years (range 4·0–16·0).

METHODS

Reticulin antibodies were measured by an indirect immunofluorescence method with some modifications[6 7] to the preliminary report.[8] Serum titres equal to or over 1:50 were considered positive. An enzyme linked immunosorbent (ELISA) method was used to determine the titre of gliadin antibodies in the sera.[9 10]

Routine small bowel biopsy was performed with an adult Watson capsule. Histologically the mucosal findings were divided into four groups: normal, partial villous atrophy, severe partial villous atrophy, and subtotal villous atrophy or flat mucosa.

Results

Twenty two patients who were negative for IgA class reticulin antibodies became positive within 0·2–2·0 years (mean 0·6). The titres varied from 1:100 to 1:4000. Fifteen of the 22 adolescents and young adults had noticed no changes in their well being and seven had experienced slight to moderate abdominal symptoms at the time of appearance of reticulin antibodies. One patient had selective IgA deficiency: she had no IgA reticulin antibodies throughout but after 0·9 years of gluten challenge she was found to be positive for IgG class reticulin antibodies (1:200). No symptoms had occurred.

In all 23 patients who were positive for reticulin antibodies a clear mucosal relapse was observed on biopsy. Seventeen patients (74%) showed small, flat intestinal mucosa, two patients showed severe partial villous atrophy, and four moderate partial villous atrophy.

One patient developed intolerable abdominal symptoms after 0·4 years on gluten challenge. She had no reticulin antibodies and the gliadin antibodies showed a slight positivity but the small bowel mucosa was normal. Despite subjective symptoms she continued the challenge and a second biopsy was performed because of the symptoms after 0·8 years on gluten challenge and the biopsy specimen showed slight partial villous atrophy. She still had no reticulin antibodies. She returned to a gluten free diet.

After two years on a gluten containing diet five patients were still negative for reticulin binding antibodies and had no symptoms. They all had a small bowel biopsy. One patient showed a flat mucosa and on retesting his serum the IgA class reticulin antibodies gave a titre of 1:10. Three girls and one boy did not relapse, and the mucosa was found to be normal. Thus four out of 38 patients (11%) showed a possible recovery from coeliac disease. All four had already undergone gluten challenge earlier in childhood at the ages of 2 to 5 and they had been on a gluten free diet before this challenge for a minimum of nine years. All nine patients with late initial diagnosis undergoing their first challenge relapsed.

IgA class gliadin antibodies were measured in all the sera. In 17 patients (59%) the gliadin antibodies rose to positive levels concomitant with reticulin antibodies, and in two cases eight to 11 months earlier. In four patients the gliadin antibody titre varied back and forth from a negative result to a positive one at the same time as the reticulin antibodies gave a negative result and in two patients IgA class gliadin antibodies remained negative during the challenge and at the time of mucosal relapse. In the four young adults fulfilling ESPGAN criteria with possible postpubertal mucosal recovery IgA class gliadin antibodies were throughout at negative levels in three and varied in one.

IgG class gliadin antibodies were at positive levels at the time of biopsy in 18 of the 23 cases with mucosal relapse. In four of these IgG class gliadin antibodies were positive before reticulin antibodies. The titres varied in two during the challenge, and four adolescents and young adults with mucosal relapse showed no IgG class gliadin antibodies. In the four cases with normal mucosa at two years of gluten challenge IgG class gliadin antibodies were not at positive levels throughout in two and were positive once in one and twice in another, but were not found to be positive later.

Discussion

To our surprise not all the patients showed permanence of the mucosal reaction to gluten. Four (11%) patients, three girls and one boy, still had a normal mucosa after two years on a normal gluten containing diet. They had all undergone a gluten challenge at a younger age and their mucosa had relapsed, so the ESPGAN criteria had been fulfilled.[1 2] This finding can be explained in two ways. First, it is possible, as Schmitz *et al* have shown,[5] that coeliac disease may disappear during adolescence in some patients, so that puberty could be a milestone in coeliac disease, changing to its currently familiar 'natural history'. Secondly, these patients could represent the extremity of normal biology, being only so called late relapsers who do not follow the 'two-year rule'. In fact, there is increasing evidence that the mucosa may deteriorate even after many years on a gluten containing diet,[11] (I Polanco, J Larrauri. Abstract presented at International Coeliac Symposium, St Bartholomew's Hospital, London, 4–6 September, 1988) showing the diagnosis of transient gluten intolerance to be incorrect at least in these cases. Our four patients will be further followed up and it may of course turn out that the challenge is life long, meaning that the coeliac disease has healed. Without the present postpubertal gluten challenge study these patients would have continued unnecessarily on their gluten free diet.

Today it can be suggested that factors other than gluten ingestion are at least sometimes needed to induce mucosal damage in coeliac disease. An intriguing candidate trigger is adenovirus, as suggested by Kagnoff *et al.*[12 13] Such possibilities should be studied more extensively. The existence of external factors could offer explanations for the reported phenomenon of coeliac disease relapse over such a large range of time,[11 14] which has been confirmed in this study.

An interesting finding in the present study was the paucity of abdominal symptoms during gluten challenge. In most cases (70%) the mucosa relapsed before any symptoms had occurred. Recently Kumar *et al* also observed that teenagers with coeliac disease not following a strict gluten free diet, and with mucosal abnormality, were clinically asymptomatic.[15] It can be assumed that many of the young adults in the present study would probably not have developed any abdominal symptoms irrespective of small, flat intestinal mucosa. Likewise in many studies dealing with adult coeliac disease it has been noticed that patients may have only mild or no abdominal symptoms, and they may not have signs of malabsorption.[16 17] This we also observed in a recent family study where 9% of first degree relatives of coeliac patients were found to have coeliac disease.[18] We encouraged the adolescents and young adults with mucosal atrophy to observe a lifelong gluten free diet even if they did not experience any symptoms at the present moment. Without a diet disease entities with symptoms and signs not commonly connected with coeliac disease,[19] or even serious complications such as malignancies,[20] may later occur. Jejunal mucosa with villous atrophy may accumulate oxidated metabolites of xenobiotics, leading to an increased risk of cancer.[21]

Our hypothesis concerning reticulin antibodies proved correct. In all but one patient we needed only one biopsy during the challenge. IgA class reticulin antibodies were the indicator and were found to be positive within one to 24 months on a gluten containing diet. Histologically a clear relapse into coeliac disease was seen even if all patients did not show flat mucosa. One patient with no symptoms had a negative reticulin antibody titre (<1:50) and showed flat mucosa at the end of the study. His serum was retested and the titre was found to be 1:10. We now start testing at 1:5 and this has not increased non-specific reactions.[7] In our family study we found positive IgA class reticulin antibody titres in 3% of the relatives with normal mucosa.[18] The hypothesis also worked in the patient with selective IgA deficiency; she developed IgG class reticulin antibodies. Thus the reticulin antibody test seems to be suitable for prediction of mucosal relapse in coeliac disease. In other studies it has been reported that several biopsies were often needed to establish the diagnosis.[14 22]

In the present study gliadin antibodies and reticulin antibodies behaved differently. In six of the patients IgA class gliadin antibody titres were positive before the reticulin antibody test showed positivity and in four of these the gliadin antibody titres decreased every now and then to negative levels. This may reflect the amount of gluten ingested. In our experience the gliadin antibodies often appear earlier than tissue autoantibodies such as reticulin antibodies. Bearing in mind our working hypothesis we did not biopsy the patients at the time of first appearance of positive levels of gliadin antibodies and therefore on the basis of this study it cannot be said to what extent gliadin antibodies reflect small bowel mucosal damage in coeliac disease. When reticulin antibodies were present later and the mucosa showed villous atrophy, however, gliadin antibodies were also at positive levels in most cases.

Should routine gluten challenge be applied in coeliac disease? According to Schmerling and Franckx it would not seem justifiable, as only a few patients with coeliac disease will not relapse after an interruption of gluten free diet.[4] If we take the development of permanent tooth enamel hypoplasia into consideration, gluten challenge should not be made before the age of 3 years. Gluten reintroduction of short duration is recommendable. The appropriate age for gluten challenge is over 7 years, when all the crowns of permanent teeth have developed.[23] In our gastroenterology unit we use gluten challenge at the age of 6 to 7 in children with a very early onset of coeliac disease or if there has been any doubt as to the accuracy of the primary diagnosis. Otherwise we have felt safe with our diagnoses based on mucosal histology and the disappearance of symptoms together with reticulin and gliadin antibodies during dietary treatment. It should be stressed that over 60% of our primary diagnoses are today made at school age and only 10% before the age of 2 years. On the other hand, when the results of the present study are considered together with the findings of Schmitz *et al*[5] routine postpubertal gluten challenge should be taken into consideration. More prospective studies are needed to ascertain the nature of coeliac disease.

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References

[1] Meeuwisse GW. Round-table discussion. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59**:461–3.

[2] McNeish AS, Harms HK, Rey J, Shmerling DH, Visakorpi JK, Walker-Smith JA. The diagnosis of coeliac disease. *Arch Dis Child* 1979;**54**:783–6.

[3] Mäki M, Kallonen K, Lähdeaho M-L, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. *Acta Paediatr Scand* 1988;**77**:408–12.

[4] Shmerling DH, Franckx J. Childhood celiac disease: a long-term analysis of relapses in 91 patients. *J Pediatr Gastroenterol Nutr* 1986;**5**:565–9.

[5] Schmitz J, Arnaud-Battandier, Jos J, Rey J. Long-term follow-up of childhood coeliac disease. Is there a natural recovery? *Pediatr Res* 1984;**18**:1054.

[6] Mäki M, Hällström O, Vesikari T, Visakorpi JK. Evaluation of a serum IgA-class reticulin antibody test for the detection of childhood celiac disease. *J Pediatr* 1984;**105**:901–5.

[7] Hällström O. Comparison of IgA-class reticulin and endomysium antibodies in coeliac disease and dermatitis herpetiformis. *Gut* 1989 (in press).

[8] Rizzetto M, Doniach D. Types of 'reticulin' antibodies detected in human sera by immunofluorescence. *J Clin Pathol* 1973;**26**:841–51.

[9] Vainio E, Kalimo K, Reunala T, Viander M, Palosuo T. Circulating IgA- and IgG-class antigliadin antibodies in dermatitis herpetiformis detected by enzyme-linked immunosorbent assay. *Arch Dermatol Res* 1983;**275**:15–8.

[10] Savilahti E, Viander M, Perkkiö M, Vainio E, Kalimo K, Reunala T. IgA gliadin antibodies: a marker of mucosal damage in childhood coeliac disease. *Lancet* 1983;**i**:320–2.

[11] Kuitunen P, Savilahti E, Verkasalo M. Late mucosal relapse in a boy with coeliac disease and cow's milk allergy. *Acta Paediatr Scand* 1986;**75**:340–2.

[12] Kagnoff MF, Austin RK, Hubert JJ, Bernardin JE, Casarda DD. Possible role for a human adenovirus in the pathogenesis of celiac disease. *J Exp Med* 1984;**160**:1544–57.

[13] Kagnoff MF, Paterson YJ, Kumar PJ, *et al*. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. *Gut* 1987;**28**:995–1001.

[14] Kumar PJ, O'Donoghue DP, Stenson K, Dawson AM. Reintroduction of gluten in adults and children with treated coeliac disease. *Gut* 1979;**20**:743–9.

[15] Kumar PJ, Walker-Smith J, Milla P, Harris G, Colyer J, Halliday R. The teenage coeliac: follow up study of 102 patients. *Arch Dis Child* 1988;**63**:916–20.

[16] Swinson CM, Levi AJ. Is coeliac disease underdiagnosed? *Br Med J* 1980;**281**:1258–60.

[17] Logan RFA, Tucker G, Rifkind EA, Heading RC, Ferguson A. Changes in clinical features of coeliac disease in adults in Edinburgh and the Lothians 1960–79. *Br Med J* 1983;**286**:95–7.

[18] Auricchio S, Mazzacca G, Tosi R, Visakorpi J, Mäki M, Polanco I. Coeliac disease as a familial condition: Identification of asymptomatic coeliac patients within family groups. *Gastroenterology International* 1988;**1**:25–31.

[19] Mulder CJJ, Tytgat GNJ. Coeliac disease and related disorders. *Neth J Med* 1987;**31**:286–99.

[20] Swinson CM, Slavin G, Coles EC, Booth CC. Coeliac disease and malignancy. *Lancet* 1983;**i**:111–5.

[21] Ståhlberg M-R, Hietanen E, Mäki M. Mucosal biotransformation rates in the small intestine of children. *Gut* 1988;**29**:1058–63.

[22] Packer SM, Charlton V, Keeling JW, *et al*. Gluten challenge in treated coeliac disease. *Arch Dis Child* 1978;**53**:449–55.

[23] Aine L. Dental enamel defects and dental maturity in children and adolescents with coeliac disease. *Proceedings of the Finnish Dental Society* 1986;**82**(suppl 3):1–71.

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Oral plasma zinc tolerance test in patients with protein energy malnutrition

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SUMMARY Zinc absorption was measured in 37 children with malnutrition using the oral zinc tolerance test (22·5 mg elementary zinc) and the results compared with those of a group of healthy control subjects. The increase in plasma zinc was significantly lower in patients with marasmic kwashiorkor than in the control group. The zinc tolerance test was, however, normal in marasmic patients.

We conclude that zinc deficiency occurs in some types of protein energy malnutrition, and that malabsorption may aggravate zinc deficiency. It is reasonable to give higher doses of zinc than are usually recommended during oral zinc supplementation in patients with protein energy malnutrition.

Protein energy malnutrition is still an important problem in many parts of the world. Certain clinical features are common to patients with protein energy malnutrition and those with zinc deficiency, including diarrhoea, anorexia, growth retardation, muscular atrophy, and a tendency to infections. This similarity has led many workers to study zinc absorption in patients with protein calorie malnutrition. Some found that plasma zinc concentrations were low,[1] and others found decreased serum zinc concentrations in malnutrition, together with skin lesions.[2 3]

Protein energy malnutrition is associated with various degrees of intestinal changes, which include gastrointestinal mucosal atrophy and structural alterations in the jejunal villi.[4–8] Apart from inadequate dietary intake, digestive and absorptive defects may be important in the aetiology of protein energy malnutrition. It is, however, difficult to say whether these defects are causes or effects of the malnutrition.

The aim of this study was to determine whether there is a decrease in intestinal absorption of zinc in protein energy malnutrition in addition to preexisting zinc deficiency and malabsorption.

Subjects and methods

Thirty seven children (19 boys and 18 girls) aged between 5 months and 5 years with protein energy malnutrition were compared with 10 healthy children (eight boys and two girls) aged between 6 months and 5 years. The patients were classified according to the McLaren system.[9]

Routine laboratory tests were performed using standard methods. Serum alkaline phosphatase activities were measured (Sigma Diagnostics), and plasma and erythrocyte zinc concentrations were assessed by an atomic absorption spectrophotometer (Perkin Elmer Model 403).[10] Blood samples (4·5 ml) were collected using zinc free materials and anticoagulated with zinc free oxalate solution. Plasma was separated by centrifugation and the plasma zinc concentration determined using 3:1 dilution of plasma. Erythrocyte zinc concentrations were determined by the method of Rosney and Gorfren.[11]

For the oral plasma zinc tolerance test blood was taken from subjects to determine fasting plasma zinc after an eight hour overnight fast. A dose of 100 mg hydrated zinc sulphate (22·5 mg elementary zinc) was then given. The subjects were allowed only water during the test. After the oral test dose of zinc, blood was drawn at one, two and four hours for measurement of plasma zinc concentrations. Using the data obtained, the increases in plasma zinc concentrations above fasting values were plotted.[13] The control group was tested in the same way.

Mean (SD) values were calculated for all measurements. Student's *t* test was used to assess the significance of differences between the groups.

Results

Thirty seven malnourished children aged 5 months to 5 years and 10 healthy control subjects aged 6 months to 5 years were studied. Thirteen children had marasmus, 18 marasmic kwashiorkor, and six kwashiorkor.

Diarrhoea was present in 22 (60%), oedema in five (14%), anal, gluteal, and oral dermatitis in 19 (52%), and hair loss in 26 (70%).

Height ($p<0·05$), weight ($p<0·01$), mid arm circumference ($p<0·001$), haemoglobin concentration ($p<0·01$), total protein and albumin ($p<0·01$), and globulin ($p<0·05$) concentrations, and alkaline phosphatase activity ($p<0·01$) were signficantly decreased in the malnourished group compared with the control group (tables 1 and 2). The decreases in serum albumin concentrations were especially prominent in the patients with marasmic kwashiorkor and kwashiorkor ($p<0·05$ and $p<0·01$, respectively).

Plasma zinc and erythrocyte zinc concentrations and the results of the oral plasma zinc tolerance tests are shown in table 3. Plasma zinc and erythrocyte zinc concentrations were significantly lower in every subgroup compared with the control group ($p<0·01$).

When patients with marasmic kwashiorkor and kwashiorkor were examined together after the zinc test dose had been given, the increase in plasma zinc was significantly less in the second hour compared with the control group ($p<0·05$). On the other hand, the increase in plasma zinc was normal in the subgroup of marasmic patients (figure).

Table 1 *Clinical and laboratory findings in 37 patients with protein energy malnutrition and 10 control subjects. Values are expressed as mean (SD)*

	Patients	*Control subjects*	*p Value*
Height (cm)	68·8 (13·4)	78·0 (9·9)	0·001
Weight (kg)	6·7 (3·2)	10·0 (3·2)	0·01
Mid arm circumference (cm)	10·4 (2·2)	15·4 (1·2)	0·05
Haemoglobin concentration (g/l)	97 (20)	117 (10)	0·01
Alkaline phosphatase activity (IU/l)	60·7 (38·8)	101·7 (39·0)	0·01
Total protein concentration (g/l)	55 (10)	69 (5)	NS
Albumin concentration (g/l)	35 (9)	43 (5)	0·01
Globulin concentration (g/l)	20 (4)	25 (7)	0·01

Table 2 *Protein concentrations (g/l) in 37 patients with protein energy malnutrition. Values are expressed as mean (SD)*

	Marasmus (n=13)	*Marasmic kwashiorkor (n=18)*	*p* Value*	*Kwashiorkor (n=6)*	*p* Value*
Total protein	61 (9)	54 (8)	0·01	43 (10)	0·001
Albumin	39 (8)	35 (8)	0·05	26 (8)	0·001
Globulin	22 (4)	20 (4)	0·001	17 (4)	0·05

*Compared with normal subjects.

Table 3 *Zinc concentrations in 37 patients with protein energy malnutrition and 10 control subjects*

	Patients				*Control subjects (n=10)*
	Marasmus (n=13)	*Marasmic kwashiorkor (n=18)*	*Kwashiorkor (n=6)*	*Total (n=37)*	
Mean (SD) fasting plasma zinc (μmol/l)	13·9 (4·6)*	15·6 (3·7)	13·0 (2·9)*	14·6 (3·8)**	18·4 (3·9)
Median (range)	13·8 (6·9–19·9)	15·1 (6·9–22·2)	12·3 (10·2–16·7)	14·4 (6·9–22·2)	19·9 (12·1–24·5)
Mean (SD) erythrocyte zinc (mg/l)	11·9 (4·3)*	8·0 (2·7)***	8·8 (0·8)**	9·6 (3·7)***	17·1 (6·0)
Median (range)	11·4 (5·4–18·9)	8·2 (4·1–12·9)	9·4 (8·2–18·1)	9·1 (4·1–21·7)	18·5 (10·4–23·9)
Mean (SD) increase in plasma zinc (μmol/l):					
At one hour	11·4 (5·8)	4·8 (4·6)**	5·8 (5·3)	7·7 (5·7)*	12·1 (7·6)
At two hours	18·2 (11·0)	10·4 (6·8)*	8·0 (7·6)*	12·1 (9·2)	17·5 (6·5)
At four hours	6·3 (5·6)	3·4 (4·2)	2·5 (3·6)	4·3 (5·6)	2·2 (4·5)

*$p<0·05$; **$p<0·01$, and ***$p<0·001$ compared with control subjects.

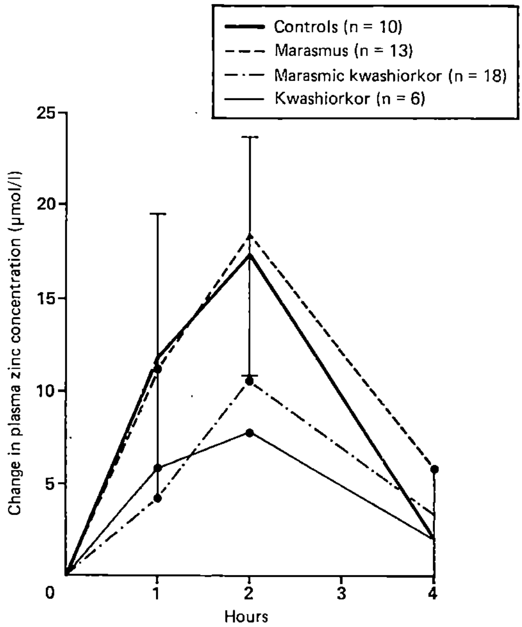

Figure *Mean (SD) plasma zinc concentrations after oral plasma zinc tolerance test in patients with protein energy malnutrition.*

Discussion

In this study alkaline phosphatase activity and plasma and erythrocyte zinc concentrations in patients with protein energy malnutrition were significantly lower than those of the control group.

There are several reports concerning zinc absorption in malnutrition. In some, zinc concentrations in plasma or serum were decreased[1 13] while in others they were reported to be normal.[2 4] Plasma zinc concentrations are not, however, good indicators of zinc state in man, because not only is plasma zinc turnover rapid, but many factors influence it.[14] In order to study zinc state, therefore, we had to determine plasma zinc and erythrocyte zinc concentrations as well as alkaline phosphatase (an important zinc metalloenzyme) activity in our subjects.[15–17]

Zinc is required for normal growth and development, and deficiency can result from inadequate dietary intake, impaired absorption, excessive excretion, or inherited defects in zinc metabolsim. Requirements depend on the weight, age, and growth rate of children, and the bioavailability of zinc from different sources. Indeed, nutritional insufficiency was one of the main reasons for zinc deficiency in our group of patients.

The mitosis rate in the cells of the gastrointestinal, immune and haematopoietic systems is high. The effects of zinc deficiency as a result of the important action of zinc on protein synthesis, therefore, are observed mostly in these systems, so it is reasonable to claim that the chronic zinc deficiency in protein energy malnutrition might lead to pathological changes in the intestinal mucosa.

Many alterations in the gastrointestinal tracts of malnourished children have been reported.[6–8] A genetic zinc deficiency disease, acrodermatitis enteropathica, causes severe intestinal mucosal atrophy, and zinc supplementation is effective in returning the mucosal to normal.

To measure intestinal zinc absorption the oral plasma zinc tolerance test was conducted in patient and control groups. The oral plasma zinc tolerance test, which measures the increase in plasma zinc concentrations, has been widely used as an assessment of intestinal zinc absorption.[19 20]

Under standard conditions the test gives valuable information about the absorption of zinc by the small intestine. Valberg *et al* compared radioactive zinc absorption with the oral plasma zinc tolerance test and found that the tests gave comparable results.[21] In both our subgroups of patients (marasmic kwashiorkor and kwashiorkor) the plasma zinc curve (figure) was significantly depressed compared with that of the control group.

In patients with marasmus, the plasma zinc tolerance test was normal, confirming the results of Brunser *et al,* who studied jejunal biopsy specimens of patients with marasmus and found normal mucosa.[7]

We conclude that zinc deficiency in patients with protein energy malnutrition can induce intestinal mucosal changes that may aggravate the zinc deficiency, thus creating a vicious circle. It is therefore reasonable to give higher doses of zinc than are usually recommended when giving oral zinc supplementation to patients with protein energy malnutrition.

References

[1] Kumar S, Rao KSJ. Plasma and erthrocyte zinc levels in protein carlorie malnutrition. *Nutrition and Metabolism* 1973;**15**:364–8.

[2] Golden BE, Golden MHN. Plasma zinc and the clinical features of malnutrition. *Am J Clin Nutr* 1979;**32**:2490–4.

[3] Golden MH. Skin breakdown in kwashiorkor response to zinc. *Lancet* 1980;i:1256.

[4] Viteri FE, Behar M, Arroyave G, Scrimshaw S. Clinical aspects of protein malnutrition. In: Munro HN, Allison JB, eds. *Mammalian protein metabolism.* New York: Academic Press, 1956:523.

[5] Gomez F, Galvan R, Cravioto J, Frenk S, Velazquez J, Pena C. Fat absorption in chronic severe malnutrition in children. *Lancet* 1956;ii:121.

[6] Mehta HC, Saini AS, Singh H, Dhatt PS. Biochemical aspects of malasorption in marasmus. *Br J Nutr* 1984;**51**:1–6.

[7] Brunser O, Reid A, Monckeburg F. Jejunal mucosa in infant malnutrition. *Am J Clin Nutr* 1968;**21**:976–83.

[8] Tandon BN, Magora M, Saraya AK, Ramalingaswami V. *Am J Clin Nutr* 1968;**21**:813–19.

[9] McLaren DS, Read WW, Pellet PC. A simple classifing the severe forms of protein-calorie malnutrition of early childhood. *Lancet* 1967;**i**:533.

[10] Perkin E. *Clinical method for atomic absorption spectroscopy.* Connecticut: Perkin Elmer, 1973.

[11] Rosnev F, Gorfren PC. Erythrocyte and plasma zinc and magnesium levels in healthy and disease. *J Lab Clin Med* 1963;**72**:213–20.

[12] Solomons NW, Jacob RA. Studies on the bioavailability of zinc in humans: effect of heme and non heme iron on the absorption of zinc. *Am J Clin Nutr* 1983;**34**:475–82.

[13] Canfield WK, Menge R, Wolravens PA, Hambridge KM. Plasma zinc values in children recovering from protein energy malnutrition. *J Pediatr* 1980;**97**:87–9.

[14] Baer MT, King JC. Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. *Am J Clin Nutr* 1984;**39**:556–9.

[15] Kasarskis EJ, Schuna A. Serum alkaline phosphatase after treatment of zinc deficiency in humans. *Am J Clin Nutr* 1980;**33**:2609–12.

[16] Reinhold JG, Kfoury A. Zinc dependent enzymes in zinc depleted rats, intestinal alkaline phosphatase. *Am J Clin Nutr* 1969;**22**:1250–1256.

[17] Weismann K, Hoyer H. Serum alkaline phosphatase activity in acrodermatitis enteropathica. An index of the serum zinc level. *Acta Derm Venereol* 1979;**59**:89–90.

[18] Kelly R, Davidson GP, Townley RRW, Campbell PE. Reversible intestinal mucosal abnormality in acrodermatitis enteropathica. *Arch Dis Child* 1976;**51**:219–22.

[19] Sullivan JF, Jetton MM, Burch RE. A zinc tolerance test. *J Lab Clin Med* 1979;**93**:485–92.

[20] Fickel JJ, Freeland-Graves JH. Zinc tolerance test in normal and zinc depleted humans. *Fed Proc* 1983;**42**:392–7.

[21] Valberg LS, Flanagan PR, Brennan J, Chamberlain MJ. Does the oral zinc tolerance test measure zinc absorption. *Am J Clin Nutr* 1985;**41**:37–42.

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Aneurysms of the vein of Galen

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SUMMARY Six neonates with aneurysms of the vein of Galen are described: five were associated with an intracerebral arteriovenous fistula and presented with heart failure in the neonatal period; one had hydrocephalus at birth. Two infants died from intractable cardiac failure within 48 hours of age and two from progressive hydrocephalus and cardiac failure at 8 months and 8 years respectively. Two of the infants had copper coil embolisation of the aneurysm—one has since died of an intracerebral haemorrhage. The diagnosis of an intracerebral arteriovenous fistula should be considered in any infant presenting with unexplained heart failure. Close attention to the volume of all arterial pulses, and the venous pulse in the neck as well as auscultation of the head for a cranial bruit may suggest the diagnosis, which can then be substantiated by cerebral ultrasound.

Aneurysms of the vein of Galen are rare congenital abnormalities that have been diagnosed more often at necropsy than in life.[1 2] There is often an associated arteriovenous malformation draining into the aneurysm. The clinical presentation depends on (a) the size of the aneurysm, which if large may compress the aqueduct of Sylvius and the posterior end of the third ventricle, causing hydrocephalus and (b) the magnitude of blood flow through any associated arteriovenous fistula. In most instances there is a large arteriovenous shunt which causes cardiac failure.

The results of surgical and non-surgical management of this latter group is extremely difficult and is associated with a high mortality. Recently, however, some success has been reported with copper coil embolisation of the aneurysms.[3] Early diagnosis is therefore necessary so that such treatment can be electively planned.

In this report we describe six cases of vein of Galen aneurysms seen in the last 15 years, four between June 1986 and April 1988, showing the various modes of presentation. The clinical signs and investigations used to establish the diagnosis are also described.

Case reports

Table 1 summarises the clinical presentation and course of the infants and table 2 shows the investigations performed.

CASE 1 (INDEX CASE)

A boy, born at full term and weighing 3200 g, was

Table 1 *Clinical presentation and course*

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
Congestive cardiac failure	+	+	–	+	+	+
Pulse volume	Peripheral ↓↓ Carotid ↑↑	Peripheral variable Carotid ↑	↑	Normal	↑	No record
Cranial bruit	+	+	–	+	+	+
Seizures	+	–	–	–	+	+
Cerebral haemorrhage	–	–	–	+*	–	–
Hydrocephalus	–	–	+	–	+	+
Outcome	Died at 2 days	Died at 1 day	Alive	Died at 3 months	Died at 8 months	Died at 8 years

+/– Present/absent; ↑ increased, ↓ decreased.
*Occurred six weeks after embolisation procedure.

Table 2 *Investigations*

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*
Electrocardiography	Normal	*	No record	Right axis deviation, right ventricular hypertrophy	Normal	Normal
Heart size by chest radiography	Increased	Increased	Normal	Increased	Increased	Increased
Two dimensional echocardiography	Increased right heart, increased carotids, patent foramen ovale, patent ductus arteriosus	Increased right heart, patent foramen ovale, heart, patent ductus arteriosus	*	Atrial septal defect	*	*
Cerebral ultrasound	Aneurysm	Aneurysm	Aneurysm, increased ventricles	Aneurysm	*	*
Cardiac catheterisation	*	*	*	Arteriovenous malformation	*	*
Cerebral angiography	*	*	Arteriovenous malformation, aneurysm	Arteriovenous malformation, aneurysm	Arteriovenous malformation, aneurysm	Arteriovenous malformation, aneurysm
Computed tomgraphy	*	*	Arteriovenous malformation, aneurysm	Aneurysm	*	*

*Not performed.

delivered vaginally to a 27 year old primigravida after an uneventful pregnancy. His Apgar scores were 2 at 1 minute, 6 at 5 minutes, and 9 at 10 minutes. He required intubation and intermittent positive pressure ventilation for five minutes. By 30 minutes he was acyanotic, and had no signs of cardiac failure, but was acidotic. His head circumference was on the 50th centile. A chest radiograph showed cardiomegaly while an electrocardiogram was within normal limits (table 2).

By 18 hours of age he had developed signs of congestive cardiac failure with very low volume peripheral pulses. A diagnosis of hypoplastic left heart was suspected and he was transferred to the cardiac unit at Our Lady's Hospital.

On examination he was an ill, lethargic, distressed baby who was grey in colour. All pulses, except the carotids, were of reduced volume. He had prominent venous and arterial neck pulsations. The heart sounds were palpable. On auscultation there was evidence of pulmonary hypertension and a gallop rhythm. A systolic ejection murmur was heard widely over the precordium, maximal at the lower left sternal border. There was a prominent continuous bruit over the neck vessels, and softer over the cranium (table 1). The clinical impression was of cardiac failure secondary to a cerebral arteriovenous malformation.

Echocardiography (table 2) showed a dilated innominate vein and superior vena cava, an enlarged right atrium and right ventricle, and large tortuous carotid arteries (fig 1). There was also a patent foramen ovale and ductus arteriosus. Cerebral ultrasound showed a large central echo free cystic lesion which displaced the lateral ventricles (fig 2).

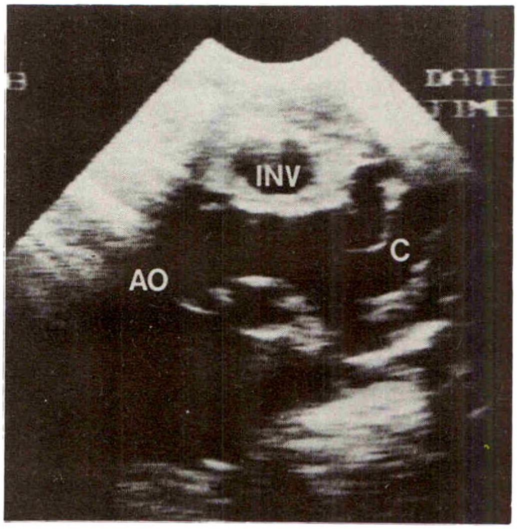

Fig 1 *Case 1. Two dimensional echocardiograph showing aortic arch (AO) with dilated tortuous carotid arteries (C) and engorged innominate vein (INV).*

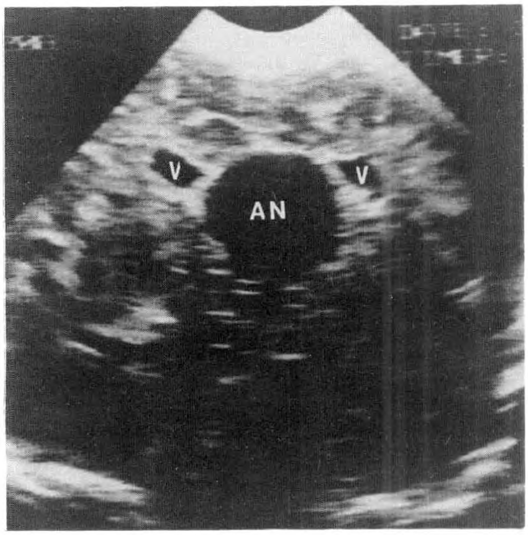

Fig 2 *Case 1. Cerebral ultrasound—short axis. Large central cystic lesion (AN) displaces lateral ventricles (V).*

Neurological and neurosurgical opinions were obtained. Surgery was not considered feasible in view of the baby's critical condition. Over the next 24 hours the baby's condition deteriorated. He had an episode of left sided twitching. He became progressively more tachypnoeic, cyanosed, and oedematous, and died at 2 days of age.

Necropsy of the brain showed that there was a large arteriovenous malformation draining into an aneurysm of the vein of Galen. The feeding arterial vessels arose from the basilar system, and the lateral, straight, and sigmoid sinuses were engorged.

CASE 2

A boy, born at full term and weighing 4300 g, was delivered vaginally to a 21 year old primigravida. There was shoulder dystocia and the Apgar scores were 4 at 1 minute and 9 at 5 minutes. Bounding pulses were noted at birth and oxygen was administered by mask because of 'poor' colour. There was facial suffusion with petechiae and central cyanosis. The infant was transferred to Our Lady's Hospital at 9 hours of age with suspected cyanotic congenital heart disease. On examination the infant was acutely ill, and lethargic with mild central cyanosis, tachypnoea, and mild dyspnoea. The head circumference was on the 90th centile but was appropriate for this infant's size. The pulse volume was normal with a slightly brisk quality but not bounding. The carotid pulse was easily felt but also not bounding. The venous pulsation in the neck was very prominent. There was a significant increase in right ventricular activity and on auscultation an ejection click and loud pulmonary closure sound indicating severe pulmonary hypertension. An ejection systolic murmur, grade III/VI in intensity, was heard widely over the precordium and a continuous murmur was easily appreciated over the carotid arteries and cranium. The liver was engorged and palpable 3·0 cm below the right costal margin. On the chest radiography there was appreciable cardiomegaly with congested lungs.

A diagnosis of a cerebral arteriovenous malformation was suspected and confirmed on cerebral ultrasound, which showed a large vein of Galen aneurysm. The echocardiogram showed a large right atrium and ventricle, mild dilatation of the innominate vein and superior vena cava. The carotid arteries were not tortuous and enlarged as in case 1. There was an associated patent ductus arteriosus and atrial septal defect. Supportive care only was given as neither surgery nor coil embolisation was considered feasible. The infant died at 24 hours of age.

CASE 3

A boy, born at full term and weighing 3800 g, was delivered vaginally after an uneventful pregnancy to a 38 year old mother of four. His Apgar scores were 9 at 1 minute and 10 at 5 minutes. Routine examination showed his head circumference to be 39 cm; this was greater than the 90th centile for his gestational age.

Cerebral ultrasound showed a central echo free cystic lesion compressing the aqueduct of Sylvius (fig 3). He was seen by the paediatric neurologist

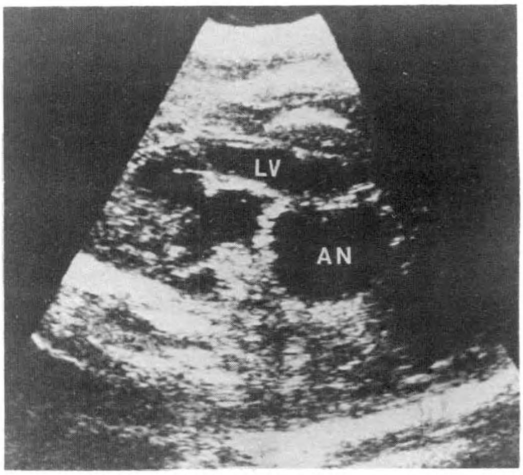

Fig 3 *Case 3. Cerebral ultrasound—long axis. Large echo free lesion (AN) and dilated lateral ventricles (LV) above.*

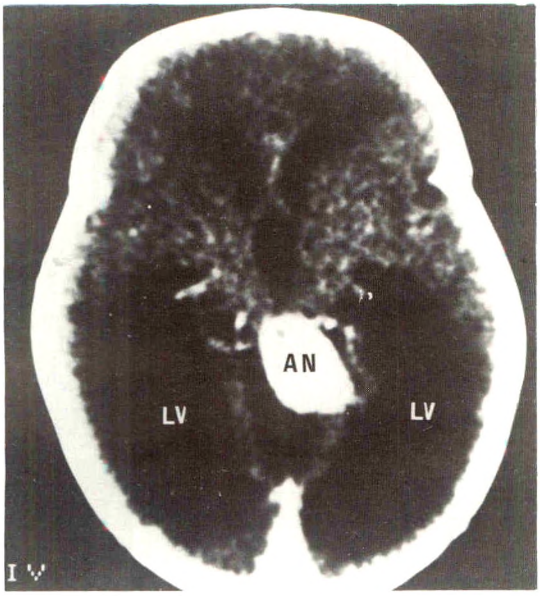

Fig 4 *Case 3. Computed tomogram with contrast, axial view. Arteriovenous malformation draining into the aneurysm (AN) of the vein of Galen, which drains into the straight sinus. The dilated lateral ventricles (LV) are also seen.*

and referred for contrast computed tomography, which confirmed hydrocephalus with dilatation of the lateral and third ventricles and an aneurysm of the vein of Galen, obstructing the aqueduct of Sylvius (fig 4). Cerebral angiography confirmed the presence of an associated small arteriovenous malformation draining into the vein of Galen. Initial neurological examination was otherwise normal.

Cardiological examination at 3 weeks of age showed signs of a hyperdynamic circulation without cardiac failure. A cranial bruit was not heard.

The baby developed progressive hydrocephalus necessitating the insertion of a ventriculoperitoneal shunt at 5 weeks of age. This was followed by the first part of a staged embolisation procedure at 6 weeks of age in which copper coils were introduced into the aneurysm under imaging intensification control.

He is clinically well at 2 years of age, apart from mild developmental delay.

CASE 4

A boy, born at full term and weighing 3270 g, was delivered vaginally to a 25 year old primigravida. His Apgar scores were 4 at 1 minute and 10 at 5 minutes.

The baby was transferred to the neonatal intensive care unit as he was tachypnoeic. He was found to be acyanotic with a head circumference greater than the 50th centile.

He became more tachypnoeic and was transferred to Our Lady's Hospital at 2 days of age. On examination he was tachnpnoeic with intercostal recession. On auscultation there was evidence of pulmonary hypertension and a systolic murmur was audible over the pulmonary area. A chest radiograph showed cardiomegaly and increased pulmonary vascularity. On an electrocardiogram right axis deviation, right atrial enlargement, and right ventricular hypertrophy were shown. Echocardiography showed an atrial septal defect of the secundum type.

He was treated with digoxin and diuretics. His tachypnoea settled initially. Over the next three weeks he continued to have episodes of tachypnoea and cyanosis. A cardiac catheterisation was performed at 4 weeks of age. An intracranial arteriovenous malformation with an aneurysm of the vein of Galen was visualised after a left ventricular angiogram (table 2).

He was seen by the paediatric neurologist. The baby's head circumference had grown along the 50th centile and a cranial bruit was heard. A central cystic lesion was seen on cerebral ultrasound.

The baby was transferred to the neurosurgical unit at another hospital where an arteriovenous malformation draining into the vein of Galen was confirmed on cerebral angiography. He had the first part of a staged embolisation procedure similar to case 3 at 6 weeks of age. At 3 months of age the baby developed seizures and died from massive intracranial haemorrhage.

CASE 5

A girl, aged 5 weeks, born in 1976 in New Zealand to Irish parents was admitted with failure to thrive and convulsions. She had been feeding poorly and was drowsy for several days before admission. The doctor who referred her to hospital witnessed episodes of fitting, staring, and stiffening, which had not been noticed by her parents.

On admission she was having frequent seizures. Her head circumference was on the 50th centile. She was acyanotic, her pulses were described as jerky, and her liver was enlarged. The precordium was hyperactive. On auscultation there was a systolic murmur along the left sternal border, and a loud cranial bruit was heard. An electrocardiogram was normal for her age. A chest radiograph showed cardiomegaly. She was treated with digoxin, diuretics, and anticonvulsants. When stable, cerebral angiography was performed at 6 weeks of age: this showed a large central arteriovenous malformation draining into an aneurysm of the vein of Galen. In consultatation with a neurologist and a neurosurgeon her lesion was considered inoperable so she was managed conservatively.

Her family moved home to Ireland soon after the diagnosis was made and she was admitted to Our Lady's Hospital. She had evidence of severe developmental delay, developed progressive hydrocephalus, and died at 8 months of age.

CASE 6

A 3 day old boy, born in 1973, was transferred from a maternity hospital with signs of cardiac failure. He was tachypnoeic, with intercostal recession and an enlarged liver. His head circumference was greater than the 50th centile. There was a systolic murmur along the left sternal edge. A chest radiograph showed cardiomegaly and evidence of pneumonia. An electrocardiogram was within normal limits for age. He was treated with digoxin, diuretics, and antibiotics to which he had a good response. He was thought to have a ventricular septal defect. When reviewed at 11 weeks of age he was well. His weight and head circumference were just above the 90th centile.

When seen at 8 months his head circumference was considerably greater than the 90th centile. His scalp veins were dilated and he had slight proptosis of his right eye. A cranial bruit was heard. He was referred to the neurosurgical unit at another hospital where he had carotid angiography: this showed an arteriovenous malformation in the region of the right lateral ventricle draining into an aneurysm of the vein of Galen. The aneurysm was obstructing the aqueduct of Sylvius.

At 13 months posterior fossa exploration was attempted with a view to ligating some of the feeding vessels, but haemorrhage was so severe that the operation was abandoned. Despite the apparently hopeless outlook after the failed surgery he survived until 8 years of age. In the intervening years he developed a progressive hemiplegia but had only mild developmental delay. He developed spastic quadriplegia in the last months of his life and died of pneumonia.

Discussion

The vein of Galen, or great cerebral vein, is formed by the union of the two internal cerebral veins. It drains into the straight sinus. Arteriovenous malformations are congenital vascular anomalies that vary greatly in size. They consist of a convoluted mass of blood vessels fed by large arteries and drained by increasingly large veins. Aneurysmal dilatation of the vein of Galen occurs when one or more abnormal arteries connect directly into it. As a result of this arteriovenous connection a shunt is established. This lesion is quite different from arteriovenous malformations elsewhere in the brain, where aneurysmal dilatation of the draining veins does not occur.

Arteriovenous malformations may present with symptoms at any age from infancy to the sixth or seventh decade but most commonly cause problems in the age group of 25 to 35 years. The initial manifestations are usually haemorrhage in about 50% of cases, seizures in 25 to 30%, focal neurologic deficit in 3 to 5%, and recurrent headaches in about 5%.[4] When the presentation occurs in infancy, however, and especially in the newborn, the arteriovenous malformation is usually associated with an aneurysm of the vein of Galen and because there is usually a large blood flow through the consequent arteriovenous fistula, heart failure dominates the clinical presentation.[3 5–8] This presentation was evident in five of the six children who were admitted to this hospital. If the infant survives and if the magnitude of blood flow through the fistulous communication is not large, the aneurysm of the vein of Galen may obstruct the aqueduct of Sylvius leading to hydrocephalus. Case 3 was unusual in that hydrocephalus was evident at birth. Older children may present with headaches, focal seizures, or subarachnoid haemorrhage. Intraventricular haemorrhage is a rare complication.[9] Intracranial haemorrhage occurred in only one of our cases and that event happened six weeks after embolisation treatment.

The clinical diagnosis of a cerebral arteriovenous fistula as a cause of congestive cardiac failure in the newborn may be difficult but is possible if close attention is paid to certain crucial clinical signs. Bilateral prominent venous and arterial pulsations in the neck were clearly evident in our recent cases and may have been present in the earlier cases though not noted. These clinical signs may be overlooked in the neonate because of the short neck and the laxity of the tissues in this area, unless the infant is propped up and the head extended. The importance of palpating the carotid pulse is highlighted by the often fluctuating volume of the peripheral pulses. While the peripheral pulse is usually described as bounding in quality there may be considerable variation between cases as well as in the individual case at different times (for example, case 2). In case 1 the volume of the peripheral pulse was so poor that the hypoplastic left heart syndrome was suspected until the bounding carotid pulse was appreciated. This cardiocerebral steal was also evident in case 2, though to a lesser degree. The cranial bruit is the other important clinical sign and was noted in five of the six infants described. According to Hughes a benign systolic cranial bruit may be found in 15% of normal infants and children under the age of 5 years.[10] The cranial bruit in the presence of an arteriovenous malformation, however, is continuous and while usually soft is audible dominantly over the parietal areas of the skull and may be heard over most of the posterior cranial vault. The continuous bruit may also be noted over the neck vessels.

When the diagnosis is suspected clinically two dimensional ultrasound, with or without contrast of the heart and brain, provides a rapid and efficient method for the detection of an aneurysm of the vein of Galen.[2] Echocardiography may help to exclude a structural cardiac defect and indirectly suggest the possibility of the diagnosis of a cerebral arteriovenous malformation by the observation of a dilated innominate vein, superior vena cava, and enlarged tortuous carotid arteries, which have increased pulsation. Cranial ultrasound clearly shows the aneurysm of the vein of Galen as an echo free space, which, if compressing the aqueduct of Sylvius will be associated with dilatation of the lateral ventricles as shown in case 3. Selective arteriograms or computerised tomography may be reserved for detailed anatomical studies of the arteriovenous malformation before surgery.

Surgery for this condition is difficult and rarely successful, though there have been some encouraging results recently.[2 5 6] The two main approaches are obliteration of the feeding vessels and the use of emboli. Mickle and Quisling described the procedure in which vein of Galen aneurysms are embolised with copper coils.[3] Two of their three patients had a satisfactory outcome, and one of our patients is clinically well, though with mild developmental delay two years after the procedure.

While the newborn infant continues to pose major management problems, early diagnosis of the malformation is essential if a planned surgical or embolic approach, or both, is to be undertaken before the infant is in a critical state. Close attention to clinical signs and the use of echocardiography and cerebral ultrasound should facilitate an early and definitive diagnosis of this rare though important anomaly.

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References

[1] Norman MG, Beckler LE. Cerebral damage in neonates resulting from arteriovenous malformation of the vein of Galen. *J Neurol Neurosurg Psychiatry* 1974;**37**:253–8.

[2] Snider AR, Scott JS, Silverman NH. Detection of intracranial arteriovenous fistula by two dimensional ultrasound. *Circulation* 1981;**63**:1179–85.

[3] Mickle JP, Quisling RG. The transtorcular embolization of Galen aneurysms. *J Neurosurg* 1986;**64**:731–5.

[4] Kelly DL. Arteriovenous malformations of the brain. Current concepts of cerebrovascular disease. *Stroke* 1972;**7**:7–9.

[5] Hoffman HJ, Chuang S, Hendrick EB, *et al.* Aneurysm of the vein of Galen. Experience at the Hospital for Sick Children Toronto. *J Neurosurg* 1982;**57**:316–22.

[6] Claireaux AE, Newman CGH. Arteriovenous aneurysm of the great vein of Galen with heart failure in the neonatal period. *Arch Dis Child* 1960;**35**:605–12.

[7] Watson DG, Smith RR, Brann AW. Arteriovenous malformation of the vein of Galen. *Am J Dis Child* 1976;**130**:520–5.

[8] Holden AM, Fyler DC, Shillito J, *et al.* Congestive heart failure from intracranial arteriovenous fistula in infancy. *Pediatrics* 1972;**48**:30–9.

[9] Schum TR, Meyer GA, Grausz JP, Glaspey JC. Neonatal intraventricular haemorrhage due to an intracranial arteriovenous malformation—a case report. *Pediatrics* 1979;**64**:242–4.

[10] Hughes R, Todd RM. Intracranial bruits in infants and children. *Arch Dis Child* 1953;**28**:198.

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Anorectal malformations with sacral bony abnormalities

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SUMMARY A range of anorectal malformations with sacral bony abnormalities was found in members from three generations of two kindreds. The anorectal anomaly was low in all but one of the patients. Partial sacral agenesis was the main bony defect in one family, and meningomyelocele and spina bifida occulta were noted in the second. The inheritance pattern in these kinships is autosomal dominant. This may be a variant of caudal regression syndrome, which seems to be aetiologically heterogeneous.

Anorectal malformations are a group of anomalies with an estimated incidence of one in 5000 live births.[1] This congenital anomaly can be associated with bony defects in the sacrum. The bony defect varies from partial to complete sacral agenesis, to spina bifida occulta, or meningomyelocele. We describe subjects from two families each affected with an anorectal anomaly and a bony defect of the sacrum segregating in an autosomal dominant manner.

Documentation of these kinships is important in view of the clinical and genetic implications. We also discuss the aetiological heterogeneity of these congenital anomalies, which may be part of the caudal regression or dysplasia syndrome.[2]

Subjects

FAMILY A

The details of family A (fig 1) were obtained from the medical records of the paediatric surgical unit at this hospital. Two of the six brothers (II.2 and II.3) had low anorectal anomalies with partial sacral agenesis in one (II.3). Three (II.1, II.4, and II.5) had radiological evidence of partial sacral agenesis. II.1 also had left hemiparesis and scoliosis. Both children of II.4 had low anorectal anomalies and partial sacral agenesis. Four of the five children fathered by II.5 had low anorectal anomalies (III.4 and III.7). Radiological examination showed that four children had normal sacrums (III.3, III.5, III.6, and III.7). The grandparents of these siblings did not give consent for radiological examination, but have no history of anorectal anomalies or symptoms suggestive of any bony defect.

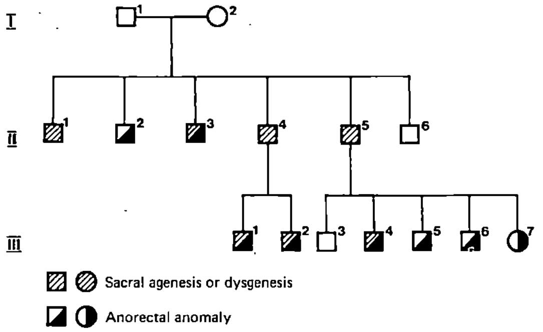

Fig 1 *Pedigree of family A.*

FAMILY B

The proband III.2 (fig 2) was referred for genetic counselling because of a low anorectal anomaly and a family history of neural tube defects. She also had a bicornuate uterus, spina bifida occulta, and a duplex left kidney. Her first pregnancy (IV.1) resulted in a male infant who died 16 hours after birth of complications of a lumbosacral meningomyelocele. Her second son (IV.2) was born with a high anorectal anomaly that was treated first by formation of a colostomy and then by an anorectal pull through operation. Radiological examination showed a spina bifida occulta of the upper sacrum. The proband's father (II.4) and mother (II.3) were normal. The proband's only sibling (III.3) is in good health and has two normal, healthy children (IV.4 and IV.5). One of the father's sisters (II.7) died in early infancy from complications associated with an anorectal anomaly, and a brother (II.9) died at the

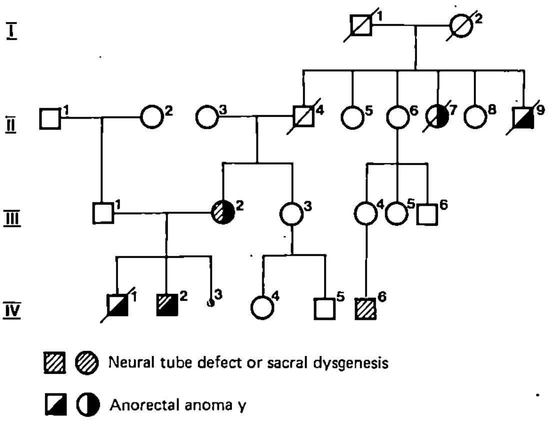

Fig 2 *Pedigree of family B.*

age of 7 hours with an open meningomyelocele. A second cousin of IV.2 (IV.6) also had a spina bifida occulta of the lower spine.

Discussion

Although congenital anorectal anomalies as a group are fairly common, there is a wide range of varieties. All the patients, except one child, in these two families had low anorectal anomalities. Partial sacral agenesis predominated in the first family, and spina bifida occulta in the second family. Meningomyelocele can be anterior and presents as a mass in the pelvic cavity. The lack of a positive family history of maternal diabetes reduces the possibility of an environmental factor for sacral agenesis or dysgenesis.

Segregation of the anorectal anomalies and the partial sacral agenesis in these two kinships is an indication of an autosomal dominant inheritance with complete penetrance and variable expression. Male to male expression excludes X linked inheritance. Although there are published examples that support the genetic aetiology for anorectal anomalies and sacral agenesis occurring independently,[3] concurrent familial occurrence of these two anomalies is rare. Autosomal dominant inheritance has also been proposed for sacral agenesis.[4]

Welch and Aterman suggested that the syndrome of caudal dysplasia should be distinguished from familial sacral agenesis.[5] Fellous *et al* reported an association between sacral agenesis and spina bifida occulta or aperta, or both, in a five generation pedigree, suggesting an autosomal dominant inheritance.[6] In the same pedigree, segregation and linkage studies using a number of genetic polymorphisms, including the human leucocyte antigens, favoured a major dominant gene for the sacral agenesis in association with spina bifida aperta. When examined for spina bifida occulta, the evidence in favour of mendelian inheritance was less convincing. These authors believe that the major dominant gene determining the sacral agenesis is similar to the mouse 'T' locus, which is the dominant tail length determining gene located on chromosome 17 approximately 15 cM from the H2 locus. (The mouse H2 gene complex is equivalent to the human leucocyte antigen gene complex on the short arm of chromosome 6.) In mice, unlike humans, it is not the dominant mutation 'T' but the recessive 't' alleles that determine the length of the tail; the dominant 'T' is lethal in the homozygotes. In some pedigrees of familial sacral agenesis, the inheritance pattern is autosomal recessive suggesting genetic heterogeneity.[7 8]

In searching published work we found only one report (by Aaronson in 1970[7]) who described a family with concurrent anorectal anomalies and partial sacral agenesis. Similarly, in pedigrees with anorectal anomalies segregating in an autosomal dominant pattern, we found no evidence of association with sacral agenesis, partial or complete.[9]

That the anorectal anomalies and sacral bony defects are aetiologically related may be explained on the basis of a defect of the caudal notochord during the first few weeks of embryogenesis. An incomplete separation may result in a low anorectal anomaly, a sacral bony defect, and a presacral mass that could be meningocele, teratoma, or duplication cyst.[10] This association has been called the 'Currarino triad'.[11] These varieties of anomalies can be described under the title of caudal regression syndrome.

In conclusion, the two kinships described in this paper provide strong evidence of an autosomal dominant pattern for the combined anorectal and sacral bony defects. It is important to obtain radiographs of the lumbosacral spine in all babies with anorectal anomalies. Partial sacral agenesis may explain incontinence of urine and stool in patients with low anorectal anomalies. We believe that genetic counselling is likely to offer help and advice to families with such a group of anomalies, and clinicians should be aware of the association between anorectal malformations and partial sacral agenesis and its dominant pattern of inheritance.

References

[1] Parkkulainen KV. Sacrococcygeal and urological anomalies in connection with congenital malformations of anus and rectum. A preliminary report. *Annales Paediatriae Fenniae (Helsinki)* 1957;**3**:51–7.

[2] Jones KL. Caudal dysplasia sequence. *Smith's recognizable patterns of human malformations.* 4th ed. Philadelphia: WB Saunders, 1988:574–5.
[3] McKusick VA. *Mendelian inheritance in man.* 8th ed. Baltimore: Johns Hopkins University Press, 1988.
[4] Say B, Coldwell JG. Hereditary defect of the sacrum. *Humangenetik* 1975;**27**:231–4.
[5] Welch JP, Aterman K. The syndrome of caudal dysplasia: a review, including etiologic considerations and evidence of heterogeneity. *Pediatr Pathol* 1984;**2**:313–27.
[6] Fellous M, Boue J, Malbrunot C, *et al.* A five generation family with sacral agenesis and spina bifida: possible similarities with the mouse T-locus. *Am J Med Genet* 1982;**12**:465–87.
[7] Aaronson I. Anterior sacral meningocele, anal canal duplication cyst and covered anus occurring in one family. *J Pediatr Surg* 1970;**5**:559–63.
[8] Finer NN, Bowen P, Dunbar LG. Caudal regression anomalad (sacral agenesis in siblings). *Clin Genet* 1978;**13**:353–8.
[9] Kaijser KA, Malstrom-Groth A. Ano-rectal abnormalities as a congenital familial incidence. *Acta Paediatrica (Uppsala)* 1957; **46**:199–200.
[10] Currarino G, Coln D, Moteler T. Triad of anorectal, sacral and presacral anomalies. *AJR* 1981;**137**:395–8.
[11] Kirks DR, Morten DF, Filston HC, Oakes WJ. The Currarino triad: complex of anorectal malformations, sacral bony abnormality, and presacral mass. *Pediatr Radiol* 1984;**14**:220–5.

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Iron supplements for preterm or low birthweight infants

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SUMMARY A survey of 57 neonatal units in the United Kingdom showed considerable disparity in iron supplementation policies for preterm low birthweight infants.

The 'ideal' intake of iron for low birthweight infants has not been established. To determine the variation in policies for iron supplementation we investigated current practices for supplementation of low birthweight infants in some neonatal units in the United Kingdom.

Methods

One neonatal unit from each regional health authority and all units attached to medical schools in the United Kingdom[1] were questioned about their policy on iron supplementation for low birthweight and preterm infants.

Results

Fifty seven units (80% of those approached) responded: 31 from teaching hospitals and 26 from district general hospitals. Four units, all from teaching hospitals, gave no routine supplements, otherwise there were no differences in the policies of teaching and non-teaching centres.

SELECTION

In 28 units gestational age was the criterion for supplementation: 22 units supplemented infants of less than 36 weeks' gestation, four selected those below 35 weeks, and one each used gestations of less than 34 weeks and 32 weeks. Thirteen units used birth weight as the criterion, with a variety of thresholds from 1500 g to 2500 g. Eleven units used a combination of these age and weight criteria. One unit supplemented every infant admitted to it.

TIME OF STARTING

Three units began supplements at 14 days postnatal age, 11 at 21 days, 24 at 28 days, nine at 42 days, and two units waited until eight and 10 weeks respectively. Criteria such as achieving feeds every four hours or a postconceptional age of 36 weeks were used by three units. One centre introduced extra iron at 14 days in infants of birth weight greater than 1200 g and at 28 days in lighter infants.

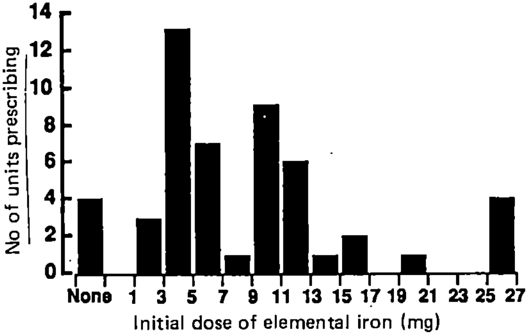

Figure *Initial dose of elemental iron prescribed (1 mg=18 μmol of iron).*

DOSE

Forty seven units prescribed a constant dose of iron irrespective of the weight or postconceptional age of eligible infants (figure); there was a nine fold variation in dose among these units (54-4923 μmol daily).

Of six units not shown in the figure, one adjusted the dose according to postnatal age and five according to body weight, either from the onset of supplementation or at discharge. These doses ranged from 16–107 μmol/kg/day.

There was no difference in the time of introducing supplements between units using higher or lower doses.

DURATION

Twenty one units advised that supplements should be continued until 6 months, and six until at least 1 year of age. Nineteen units recommended supplementation until the introduction of 'mixed feeds' or until the infants were 'fully weaned'. These latter terms were not defined. Most units thought that supplements were continued until around 6 months of age. Other criteria for stopping extra iron included reaching postconceptional ages ranging from 40 to 48 weeks or discharge.

Many units stressed that they were not able to verify whether their advice was being followed in the community.

IRON PREPARATIONS

Twenty four units used sodium ironedetate; nine prescribed polysaccharide-iron complex; eight ferrous sulphate; six ferrous fumarate; three ferrous succinate; two ferrous glycine sulphate, and one unit used ferric ammonium citrate.

Discussion

Despite the difficulties of formulating a policy for such a heterogeneous group, expert committees have produced similar recommendations for routine iron supplementation of low birthweight and preterm infants which at least provide a reference for practice.[2] None the less there is considerable variation in such practices among neonatal units in the United Kingdom.

Low birthweight infants depend on dietary iron because of their limited iron endowment at birth and high requirements for growth. Without adequate exogenous iron, a 1000 g infant will become iron deficient by the time of doubling its birth weight.[2] A daily intake of 36 μmol/kg elemental iron, however, was sufficient to prevent iron deficiency in non-transfused infants of birth weight 1000–2000 g who were receiving minimal dietary iron.[3]

During the changes of iron and haemoglobin metabolism of the first six to eight weeks of life, iron supplementation may not be needed[2 4]; furthermore at this time significant extra iron may be obtained from blood transfusions. Two units who prescribe no routine iron supplements maintain haemoglobin concentrations with transfusions.

A total daily iron intake, from all sources, of 36–54 μmol/kg, with a maximum of 270 μmol elemental iron has been recommended for low birthweight infants, by 6–8 weeks of age.

Human milk alone, despite the more efficient absorption of its iron[5] cannot meet these recommendations, but iron fortified formulas may do so thereby obviating any need for supplements. However only four units commented that their supplementation policies differentiated between breast fed and formula fed infants.

At least seven units give more than the recommended upper limit of iron,[2] and some exceed the supplement (72 μmol/kg/day) advocated by Siimes and Jarvenpaa.[6]

Thus taking the extremes of feeding and supplementation practice, the total iron intakes of an infant weighing 1500 g at birth could range from 0·3 to 20·1 mmol during the first two months of life. Postponing the introduction of supplements until 6–8 weeks of age and adjusting the dose according to body weight may avoid the theoretical risk of iron overload, but may cause difficulties in implementation, particularly after discharge. As mixed feeding may not provide adequate iron until 12–15 months of age it is suggested that supplements may be required until this time.[2]

Detailed evaluation of these different policies with more prolonged infant follow up would be needed before the clinical implications of this variability in iron supplementation are known.

We thank the units who helped in this survey, and the Grampian Area Health Board Medical Endowment Funds, and Nutricia for financial support.

References

[1] *The directory of emergency and special care units*. St Ives, Cambridgeshire: CMA Medical Data Ltd, 1987.

[2] Wharton BA, chairman. Iron. *Nutrition and feeding of preterm infants*. Oxford: Blackwell Scientific Publications, 1987:133–42.

[3] Lundstrom L, Siimes MA, Dallman PR. At what age does iron supplementation become necessary in low-birth-weight infants? *J Pediatr* 1977;**91**:878–83.

[4] Dauncey MJ, Davies CB, Shaw JCL, Urman J. The effect of iron supplements and blood transfusion on iron absorption by low birth weight infants fed pasteurised human breast milk. *Pediatr Res* 1978;**12**:899–904.

[5] Schulz-Lell G, Buss R, Oldigs H-R, Dorner K, Schaub J. Iron balances in infant nutrition. *Acta Paediatr Scand* 1987;**76**: 585–91.

[6] Siimes MA, Jarvenpaa A-L. Prevention of anaemia and iron deficiency in very low-birth-weight infants. *J Pediatr* 1982;**101**:277–80.

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Intestinal obstruction caused by malrotation of the gut in atrial isomerism

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SUMMARY Five children with atrial isomerism developed intestinal obstruction caused by malrotation of the gut. Other than asplenia, the extracardiac anomalies in these syndromes are rarely regarded as important as the outcome after intestinal surgery is poor. As cardiac treatment improves, early investigation and intervention for intestinal symptoms becomes more important.

Children with atrial isomerism usually have other severe cardiac abnormalities that dominate their clinical presentation. Associated thoracic and visceral heterotaxia were originally recognised at necropsy and have been described as 'the cardiosplenic syndrome'.[1] Apart from asplenia, however, the visceral abnormalities have been considered predominantly of pathological interest. We report five patients with atrial isomerism and severe cardiac disease in whom the clinical course was complicated by intestinal obstruction caused by malrotation of the gut.

Patients

Between 1980 and 1988 five patients with atrial isomerism developed intestinal obstruction as a result of malrotation of the gut; details of the individual cases are given in the table. All five started vomiting within six weeks of birth; the vomit was bile stained in four, the fifth having pyloric atresia as well as malrotation, and all required operation to relieve the obstruction. Two children, both without spleens, died of septic complications within three weeks of operation. One had a further episode of intestinal obstruction caused by adhesions at the age of 14 months and died six months later from his cardiac disease. Another died of bronchiolitis and cardiac failure at 11 weeks of age. One child remains well at the age of 8 years on long term treatment with antibiotics after one abdominal and three cardiac operations.

Discussion

Right atrial isomerism with asplenia is reported to

Table *Five cases of atrial isomerism with intestinal malrotation*

Case No	*Sex*	*Gestation (weeks)*	*Birth weight (g)*	*Cardiac anomalies*	*Visceral anomalies*	*Operations*	*Outcome*
1	Male	42	3770	Left atrial isomerism, double outlet right ventricle, bilateral superior vena cava, complete atrioventricular septal defect, patent ductus arteriosus	Symmetrical liver, gall bladder in midline, spleen on right and splenunculus, duodenojejunal flexure to left of midline, Ladd's transduodenal band, colon on right	Pulmonary banding, ligation of ductus, Ladd's procedure, duodenal fixation	Died at 20 months, cardiac failure
2	Female	34	1880	Double inlet left ventricle with double outlet, right atrial isomerism, pulmonary atresia	Spleen absent, stomach on left, pyloric atresia, duodenum and duodenojejunal flexure to right of midline, caecum in midabdomen, complete malrotation	Gastroduodenostomy, gastrostomy	Died at 14 days, septicaemia
3	Male	38	1740	Right atrial isomerism, complete atrioventricular septal defect with common atrioventricular valve, patent ductus arteriosus, pulmonary atresia	Symmetrical liver, gall bladder in midline, absent spleen, portal vein anterior to first part of duodenum, malrotation with common mesentery, meconium ileus, microcolon, perforated terminal ileum	Ladd's procedure ileal resection, split ileostomy	Died at 26 days, necrotising enterocolitis
4	Male	38	3080	Dextrocardia, left atrial isomerism, complete atrioventricular septal defect	Situs inversus, symmetrical liver, spleen present, malrotation with Ladd's transduodenal band	Ladd's procedure, pulmonary banding	Died at 11 weeks, cardiac failure. bronchiolitis
5	Male	41	4220	Right atrial isomerism, double outlet right ventricle, complete atrioventricular septal defect, pulmonary atresia	Spleen absent, symmetrical liver, gall bladder on right, portal vein and common bile duct anterior to first part of duodenum, Ladd's tranduodenal band, malrotation with common mesentery	Right Blalock shunt, Ladd's procedure, left Blalock shunt, Waterston shunt	Well at 8 years

represent 1% of congenital heart disease.[1] Deanfield *et al* found a 10% incidence of thoracic heterotaxy in children admitted to a cardiac unit,[2] and thoracic heterotaxy is thought to be more commonly associated with atrial isomerism than visceral heterotaxia. In studies of large numbers of cases severe cardiac disease still dominates the picture of atrial isomerism and, although recognised, extracardiac abnormalities are rarely reported as causing clinical problems.[3] Rose *et al*, in a study of 60 patients with atrial isomerism, noted only two patients with appreciable gastrointestinal abnormalities other than asplenia.[4] Moller *et al*, however, found that malrotation was always present in children with congenital heart disease who also had asplenia or polysplenia, though it occurred in less than 1% of cases in which the spleen was normal.[5] Freedom concentrated on extracardiac problems and, in 23 cases, found 25% with important gastrointestinal and genitourinary anomalies.[6] Three patients in his series presented with intestinal obstruction: two each had an annular pancreas and one had congenital fibrous bands. No child in his series with malrotation presented with obstruction.

Our collection of five children all had visceral heterotaxia and developed clinical intestinal obstruction. All had malrotation and four required division of Ladd's transduodenal band. Two had other appreciable gastrointestinal abnormalities that probably contributed to their deaths, but—as might be expected—intestinal operations seem to carry much greater risks in this group of children than in those with normal hearts. The poor survival in this group confirms other reports,[4] but one child remains well at the age of 8 years on long term treatment with antibiotics. Antipneumococcal vaccine is no use in congenital asplenia until the age of 2 years, but lifelong prophylaxis with half doses of phenoxymethylpenicillin is recommended. These children present early with serious cardiac problems, although in our unit antenatal diagnosis is becoming increasingly common. As treatment of these cardiac problems becomes more successful, the extracardiac associations become more important. Thus the occurrence of gastrointestinal symptoms (particularly bile stained vomiting) in infants with atrial isomerism warrants early investigation and consideration of operation.

References

[1] Rowe RD, Freedom RM, Mehrizi A, Bloom KR. The cardiosplenic syndromes. In: Rowe RD, ed. *The neonate with congenital heart disease.* 2nd ed. London: WB Saunders, 1981: 480–502.

[2] Deanfield JE, Leanage R, Stroobant J, Chrispin AR, Taylor JFN, Macartney FJ. Use of high kilovoltage filtered beam radiographs for detection of bronchial situs in infants and young children. *Br Heart J* 1980;**44**:577–83.

[3] Chiu I, How S, Wang J, *et al.* Clinical implications of atrial isomerism. *Br Heart J* 1988;**60**:72–7.

[4] Rose V Izukawa T, Moës CAF. Syndromes of asplenia and polysplenia. *Br Heart J* 1975;**37**:840–52.

[5] Moller JH, Amplatz K, Wolfson J. Malrotation of the bowel in patients with congenital heart disease associated with splenic anomalies. *Radiology* 1971;**99**:393–8.

[6] Freedom RM. The asplenia syndrome: a review of significant extracardiac structural abnormalities in 29 necropsied patients. *J Pediatr* 1972;**81**:1130–3.

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Comforters and night waking

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SUMMARY Among 320 low birthweight infants seen at nine months post term those using a soft object, thumb, or fingers as comforter were significantly less likely to wake at night (9/96, 9%) than those with no comforter or using a dummy (66/224, 29%). Dummy users were as likely to wake (27/93, 29%) as those without a comforter (39/131, 30%).

One of the commonest reasons for parents to seek professional advice is that their child wakes them at night. Sleep disturbance can cause serious family problems and many strategies have been advocated to alleviate the problems.[1] One of us (CJM) observed that children who were able to soothe themselves with a thumb or cloth were least likely to wake their parents at night.

In a survey of 3 year old children, Graham and Boniface[2] found that children who used an 'attachment object',[3] settled to sleep more easily than those without one (p=0·07), but they found no

Table 1 *Frequency of night waking and use of comforters*

	Type of comforter			
	None	*Dummy*	*Thumb or fingers*	*Soft object*
Total No	131	93	72	24*
No (%) not waking	92 (70)	66 (71)	64 (89)	23 (96)
No (%) waking once	24 (13)	14 (15)	3 (4)	0
No (%) waking twice or more	15 (12)	13 (14)	5 (7)	1 (4)

*Of the 24 infants categorised here as using a soft object, eight also sucked their thumb and two also used a dummy. None of these 10 children was waking at night.

relationship between thumb sucking and ease of settling. Passiman found that the security blanket was as effective as the mother in inhibiting moderate distress.[4]

This study was planned to explore the association between comforter use, comforter type, and night waking.

Patients and methods

Altogether 320 low birthweight infants who were seen at nine months post term were enrolled in this study. They were from two centres (Cambridge and Kings Lynn) of a five centre feeding trial[5] on infants with birth weights under 1850 g, born during the period 1982 to 1984. Social class, mother's education, and birth rank were coded as described elsewhere.[5] Extensive obstetric and neonatal data were recorded, the latter prospectively.

The children were seen (by RM) at nine months post term. Parents were asked how often the child woke at night and needed attention. Where this was variable, the average over the previous week was calculated and rounded up to the nearest integer. A child waking less than once a week or only when unwell was categorised as not waking. Parents were also asked whether the child had a comforter without which he did not settle to sleep. Comforters were categorised as a dummy, a special soft object, (cloth or soft toy), thumb, or fingers. We have examined for an association between the use of a comforter and night waking.

Statistical analyses were performed using the χ^2 test.

Results

Of the 320 children, 131 (41%) used no comforter, 93 (29%) used a dummy, 24 (7·5%) a special soft object, and 72 (22·5%) used thumb (n=61) or fingers (n=11). Two of the children using a soft object also used a dummy and eight were also thumb suckers. Altogether 75 (23%) were waking once or more at night and needing attention (range one to eight times).

Table 2 *Comforter use and neonatal and social factors*

	No comforter or used dummy	*Used thumb, finger, or soft object*
Total No	224	96
Mean (SD) birth weight (g)	1343 (320)	1365 (294)
Mean (SD) gestation (weeks)	30·6 (2·8)	30·7 (2·4)
No (%) boys	98 (44)	48 (50)
No (%) first child	128 (57)	59 (61)
No (%) social class 1 or 2	49 (22)	25 (26)
No (%) of mothers who chose to express breast milk	157 (70)	69 (72)

Table 1 shows the association between night waking and type of comforter. Children using a soft object, thumb, of fingers were significantly less likely to wake (9/96,9%) than those having either no comforter or a dummy (66/224, 29%; $p<0{\cdot}0005$, by χ^2). Waking was least common in those using a special soft object (1/24, 4%), though they did not differ significantly from the thumb or finger suckers, with 8/72 (11%) waking.

We considered the possibility that these two groups (those with no comforter or using a dummy compared with those using a soft object, thumb, or fingers) might differ in respect of social, obstetric, or neonatal factors, which could themselves be independently related to waking at night. Results of some analyses are shown in table 2. No associations were found with type of comforter or with night waking. The only factor significantly associated with waking was whether or not the child used a soft object, thumb, or fingers as a comforter.

Discussion

Our study demonstrated a strong association between use of a comforter and night waking at nine months post term. Those children who sucked their thumb or fingers or used a soft attachment object woke significantly less at night than the others (9% compared with 29%). Waking was least common (4%) in those who used a soft object, either alone or with another comforter. Dummy users were as likely to wake as those with no comforter.

In this group of low birthweight infants, 23% were waking and needing attention at night. This is comparable with studies on term infants that showed that 30% of 3 month old infants were waking, as were 20% of 1 to 2 year olds.[1]

The majority of children here (77%) did not disturb their parents at night. Video recordings have shown that many infants wake and fall asleep again without needing attention. One explanation for our findings would be that in the group of children who needed comforting to settle again at night, some were able to soothe themselves with a thumb or attachment object (which Bowlby regarded as substitutes for the mother), whereas the others required parental attention. Children who use effective comforters, however, may be intrinsically different and less likely to wake at night. Dummies were not effective in respect of night waking; we suggest this may be because they are easily lost.

Winnicott's work would suggest that, like thumb sucking, use of a 'transitional object' is spontaneous and cannot be deliberately initiated by parents.[6] However, there is no evidence on whether constantly providing a particular cloth might encourage a child to develop an attachment to it. Conversely, the extent to which parents can discourage attachment object use, when they dislike the practice, is not known. If further research indicated that use of a special soft object could be encouraged and could decrease night waking, this might prove to be of considerable value in families where there has been a problem with sleep disturbance.

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References

[1] Richman N. Sleep problems in young children. *Arch Dis Child* 1981;**56**:491–3.

[2] Boniface D, Graham P. The three-year-old and his attachment to a special soft object. *J Child Psychol Psychiatry* 1979;**20**: 217–24.

[3] Bowlby J. Attachment. *Attachment and loss.* Vol 1. London: Hogarth Press, 1969:309–13.

[4] Passiman RH. Providing attachment objects to facilitate learning and reduce distress: effects of mothers and security blankets. *Developmental Psychology* 1977;**13**:25–8.

[5] Morley R, Cole TJ, Powell R, *et al.* Mother's choice to provide breast milk and developmental outcome. *Arch Dis Child* 1988;**63**:1382–5.

[6] Winnicott DW. Transitional objects and transitional phenomena. *Int J Psychoanal* 1965;**34**:89–97.

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As sick as a pigeon—psittacosis myelitis

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SUMMARY An association between acute transverse myelitis and psittacosis in a teenage boy is described. Closer collaboration between doctors and vets might have made the diagnosis sooner. A full paediatric history should include details of contact with pets and other animals.

Sudden onset of paraparesis is uncommon in children; the differential diagnosis includes trauma, vascular malformation, Guillain–Barré syndrome, transverse myelitis, or cord compression. Psittacosis has been implicated in the Guillain–Barré syndrome in four reported cases,[1] but we are unaware of any published association between psittacosis and acute transverse myelitis.

Case report

A previously healthy 15 year old boy developed coryza and sore throat followed by a productive cough with purulent sputum. Eight days later he developed sudden onset of paraesthesia and leg weakness. On arrival at hospital three hours later he had weak flexion and extension of hips and knees, with a flaccid paralysis below the knees, and absent lower limb reflexes. Abdominal reflexes were present. Sensation (including proprioception and vibration) was impaired below L2.

Over the next six days he developed complete loss of sphincter control and his sensory deficit extended to T11. He also developed severe back and abdominal pain that required pethidine for two weeks.

Haemoglobin concentration, white cell count, and sedimentation rate were normal. His cerebrospinal fluid contained polymorphs at 1/µl with a protein content of 0·42 g/l, and a normal glucose concentration. No bacteria were grown. Spinal radiography and myelography gave normal results. Paired sera showed low or absent titres with no rise in antibodies against measles, rubella, varicella, mumps, herpes, cytomegalovirus, or Epstein-Barr or polio viruses. Tests for syphilis were not done.

He made a very slow recovery complicated by painful muscle contractions and segmental hyperaesthesia, which, together with urinary incontinence, contributed to a reactive depression. Eight months after onset, while still in hospital, he became profoundly preoccupied with his own death, which he was convinced would be imminent 'because that's what happened to the birds'.

It transpired that his father, a bird fancier, had lost two budgerigars and 10 racing pigeons during the previous year. All had developed a clinical syndrome of ataxia and limb paralysis, followed by death. The patient strongly disliked the birds and had expressed this in a direct adolescent manner. Hence he was given the household chore of cleaning out the bird cages. The parents had not considered the birds' deaths to be relevant to the boy's illness, nor had they mentioned his paralysis to their vet. The vet had diagnosed paramyxovirus infection (there was a national epidemic affecting similar birds) and provided vaccine for the remaining birds. Although birds continued to die, the family did not consult the vet again.

Necropsies of both a paralysed and an unaffected pigeon showed psittacosis in the affected bird. The patient's acute phase serum was now no longer available but serum taken at this time (that is, eight months after onset) had a psittacosis titre (complement fixation test) of 1 in 64. Repeat titres 24 months after onset were neglible. Psittacosis antibodies in the rest of the family were undetectable.

Two years on the patient has recovered some mobility and sphincter control, but still has diminished power in both legs, residual left foot drop, and considerable frequency of micturition. He now attends college full time in a wheelchair. No further improvement is expected as maximum recovery usually occurs in the first six months.[2 3]

Discussion

The association between the transverse myelitis and psittacosis in this boy is strong. It is not always easy to differentiate between transverse myelitis and Guillain-Barré syndrome but severe backpain, loss of sphincter control, and a clear sensory level made the distinction here.[3 4]

The evidence for a coexisting psittacosis infection at the onset of his illness could be questioned. A four fold increase in psittacosis complement fixation titres in the acute phase or a four fold decrease in titres in the late convalescent phase and/or complement fixation titres of 1 in 64 or more, are considered to indicate infection with *Chlamydia psittaci*.[5 6]

Psittacosis titres were not assayed in the acute phase but a chest infection at onset and an antipsittacosis titre of 1 in 64, eight months after his last exposure to infected pigeons, which dropped to unrecordable levels 24 months later are consistent with this diagnosis. It is possible, though unlikely, that the paralytic illness could have been avoided had an association been made between his respiratory symptoms and the birds' illness. The family consider themselves fortunate that no-one else was affected and they have destroyed the remaining birds.

Psittacosis was thought to arise from the psittacine family of birds only but it can arise from other birds and is now alternatively termed ornithosis. As it can also arise from other animals,[6] we have reverted to the more established name here. Affected birds characteristically show fluffed feathers, beak discharge, and diarrhoea but ducks and pigeons manifest an ataxic syndrome. The infectivity of different birds to man is striking: pigeons are poorly infective while parakeets (including budgerigars) are highly infectious. Humans are usually infected by the airborne route and the main symptoms are respiratory. Extrapulmonary manifestations include myocarditis, nephritis, thrombophlebitis, and meningoencephalitis: patients may be grossly disorientated or semicomatose often with features suggesting pyogenic meningitis. Severe diffuse headache is usually present. Children and adolescents have a milder and less specific illness so the diagnosis may be overlooked.

Psittacosis is one of the commonest zoonoses. Most wild urban birds are infected and the level of risk of human exposure may be underestimated. In puzzling or bizarre illnesses it is important to inquire about pets, animal contacts, and hobbies. Others have stressed the importance of maintaining close links between doctors and vets. This admonition clearly applies even in urban practice.

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Personal practice

Urge syndrome and urge incontinence

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Diurnal enuresis is still the common denominator for children who wet their pants. A closer look at children with daytime wetting, however, shows that there are two distinct categories: one with classic diurnal enuresis and normal bladder function, and the other with urinary incontinence caused by an 'urge syndrome', with bladder sphincter dysfunction, and a conspicuously high incidence of recurrent urinary tract infections.

Overactivity of the detrusor and urethral muscles is now an established cause for bladder sphincter dysfunction in children, and it is usually associated with symptoms such as urgency, frequency, daytime wetting, and urinary tract infections.[1-5] The symptoms of dysfunction induced by overactivity have in the past been blamed on either the detrusor muscle or the urethral closure mechanism, resulting in two different concepts of diagnosis and treatment.[6] Cystometric findings of uninhibited detrusor activity in children with recurrent urinary tract infections and urge syndrome were interpreted as persistent infantile bladder, occult neuropathic bladder, or isolated or subclinical neurogenic bladder. Accordingly, treatment consisted of rehabilitation programmes and anticholinergic drugs. Cystoscopy and voiding cystourethrography, on the other hand, showed abnormalities that were labelled as wide bladder neck anomaly or 'spinning top' urethra, distal urethral stenosis, external sphincter spasticity, or sphincter dyssynergia, popularising the concepts of urethral dysfunction and stenosis, and of urethral dilatation or urethrotomy as methods of treatment.

Urodynamic studies showing the interaction between bladder and sphincter muscles by simultaneous registration of bladder pressure and urethral sphincter activity at first added even more labels to the two controversial concepts, and widened the range of possible treatments. Recent reviews[7 8] support the idea that most labels can be brought down to patterns of bladder sphincter overactivity: in one pattern, strong uninhibitable detrusor contractions give rise to urgency and frequency early in the filling phase; in the other pattern, incomplete relaxation of striated urethral and pelvic floor muscles interrupts actual voiding and causes a *staccato* urinary flow.

As these patterns of bladder sphincter overactivity are detectable with urodynamic techniques we decided to investigate prospectively a selected group of children of school age whose presenting symptoms were persistent daytime wetting, urgency, and frequency.

Patients

Ninety girls and three boys with urge incontinence and recurrent urinary tract infections were studied. They were referred after the failure of previous attempts at treatment to a combined service of the departments of paediatric nephrology and child psychology in our University Children's Hospital. For every child a documented history of urinary tract infections was available; all the children had had full uroradiological investigations (excretory urography and voiding cystourethrography), and all results were available for review. Our part of the comprehensive evaluation consisted of psychological interviews of children and parents, of elaborate history taking with emphasis on voiding habits and urge, and of urodynamic studies.

Each urodynamic investigation consists of simultaneous recording of the bladder pressure, abdominal pressure, electromyographical activity of the external anal sphincter, and urine flow rate. Several recordings are made, both during filling of the bladder and emptying of the bladder, without anaesthesia or sedation.

Bladder filling and registration of bladder pressure are done through one small soft transurethral catheter (Charrière size 6). The catheter has a filling lumen and a microtransducer at the tip (MTC microtip transducer, PPD Hellige). The bladder is filled with a sterile 0·9% saline solution, the filling rate not exceeding 15 ml/minute. Abdominal pressure is registered with a Charrière size 4 catheter containing a microtip transducer inserted high into the rectum. The electromyographical signal from the anal sphincter (a measure for pelvic floor activity) is picked up with surface electrodes, amplified and monitored with an oscilloscope, and registered on a chart recorder together with the amplified pressure signals. The smallness and ease of operation of the microtip transducers (together with patience on the part of the investigator) are prerequisites for successful paediatric urodynamics, and when the procedure is properly explained, most children tolerate the investigation extremely well.

At or near the end of the filling phase the child is asked to cough, and to change from a supine to a standing or sitting position, so that detrusor instability may be detected. Bladder emptying is recorded with the child in the appropriate voiding position. Abdominal pressure is subtracted electronically from bladder pressure, to differentiate true detrusor activity from effects of abdominal straining. All events are recorded continuously without having to ask the child to use inappropriate 'holding manoeuvres' in the important transition phase between filling and micturition. Methods, definitions, and units conform to the standards recommended by the International Continence Society.

Signs and symptoms

Characteristically, children with the urge syndrome have sudden attacks of uninhibitable urge to void, inducing forceful compression of the urethra to avoid unwanted loss of urine[2 3 7–14] Usually the first attacks do not occur before the end of the morning. During the course of the day the attacks increase in number as well as in severity. The syndrome may have a nocturnal component too, as some children also experience sudden urge and loss of urine during the night.

The urge to void comes suddenly and unexpectedly. The sensation is so imperative that loss of urine can only be avoided by maximal compression of the urethra both by forceful contraction of all pelvic floor muscles and by external mechanical compression. Every child has his or her own method of external compression—a common one is squatting on one foot, with the heel of the foot against the perineum. This asymmetrical squat conveys a sense of elegance—it resembles an obeisance and Vincent,[9] who first described it, termed it the 'curtsey' sign. In assuming this position children often pretend that something was dropped on to the floor, or that a shoelace had become untied. Compression is sustained until the urge to void has passed, which can take up to several minutes.

Most children do not succeed completely (if at all) in countering the imperative need to void with external compression of the urethra, and more often than not some urine will escape. This loss of urine is involuntary and incomplete; it never takes the course of a complete micturition. It is a specific form of incontinence—urge incontinence.

OCCURRENCE ACCORDING TO AGE AND SEX

The urge syndrome is seldom seen in boys. The prevalence in girls aged 4 to 12 years is reported to be 1–3/1000. Parents usually state that symptoms and signs started around age 4 to 5; parental attitudes towards incontinence become less permissive at that age, however, and careful questioning may discover an earlier age for the first occurrence —often in conjunction with the first urinary tract infection.

Around puberty the prevalence starts to decrease, and in adolescence it is low. The 'female urethra syndrome' might be an adult counterpart of the urge syndrome in girls, but prospective studies are not available to prove this postulate.[15 16]

Fig 1 shows the age distribution for 93 children with urge syndrome all of whom were referred to our department of paediatric nephrology because of incontinence and recurrent urinary tract infections.

URINARY TRACT INFECTIONS

The correlation between urinary tract infections and the urge syndrome is generally accepted, but hard to specify.[1 2 4 8 17] A first infection may mark the beginning of a long series of recurrent infections and persisting symptoms of the urge syndrome; in other

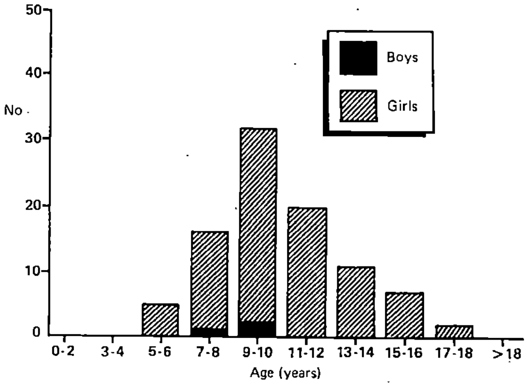

Fig 1 *Age and sex distribution of 93 children with urge syndrome and recurrent urinary tract infections who were referred for cognitive bladder training.*

cases, however, recurrent urinary tract infections seem to appear only during the course of the syndrome.

Although urinary tract infections may not constitute the primary cause of the urge syndrome they invariably occur in conjunction with the syndrome, and have a key role in the persistence and severity of its symptoms. It is probably not by chance that the prevalence of recurrent urinary tract infections and urge syndrome in girls have the same age distribution.[18]

As a consequence of this correlation, vesicoureteric reflux and reflux nephropathy also have high prevalences in children with urge syndrome.[6, 13, 14, 19–21] In the 93 children shown in fig 1, vesicoureteric reflux could be documented in 40%, and reflux nephropathy in 30% (table 1). The expected correlation between the grade of vesicoureteric reflux and the prevalence of reflux nephropathy was, however, conspicuously absent.

BEHAVIOURAL PROBLEMS

In children with long standing urge syndromes a set of secondary behavioural problems will develop (table 1). These problems can be so impressive that, at first glance, a child with urge syndrome will be diagnosed as having primary behavioural problems with 'psychogenic' enuresis.[5] Careful questioning will show that behaviour in children with urge syndrome is usually related to acceptance and understanding of their incontinence problem by peers and parents.[22]

CONSTIPATION

An urge syndrome is often associated with persistent constipation, sometimes causing faecal soiling and spurious diarrhoea. Chronic constipation is often associated with urinary tract infections and should be looked for and treated in children with urge syndrome.

Table 1 *Incidence of urinary tract infections, vesicoureteral reflux and reflux nephropathy, bladder sphincter function, and secondary behavioural problems in 93 children referred with urge syndrome and incontinence*

	No (%)
Urinary tract infections	87 (94)
Vesicoureteral reflux	37 (40)
Reflux nephropathy	28 (30)
Detrusor overactivity	42 (45)
Urethral overactivity	28 (30)
Valsalva manoeuvre	18 (19)
Normal bladder sphincter function	6 (6)
Behavioural problems	12 (13)

It is not clear whether the constipation is caused by the habit of contracting all pelvic floor muscles each time an urge to void is experienced. The association between chronic constipation and urge syndrome, first described by Vincent, merits further investigation.[9, 23]

Urodynamic findings

Urodynamic studies in children with urge syndrome have made it clear that imperative urge to void coincides with uninhibited (unstable) detrusor contractions, occurring early in the filling phase.[2, 3, 7, 8, 13, 14] Simultaneous registration of bladder pressure with electromyographical activity of the pelvic floor shows how children suppress the sudden urge by forceful contraction of all pelvic floor muscles, to

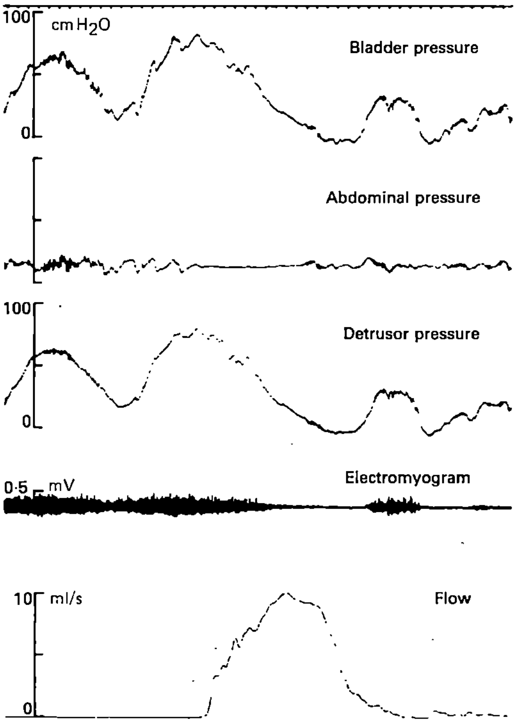

Fig 2 *Detrusor overactivity countered by pelvic floor contractions (measured by electromyography) in a 5 year old girl with recurrent urinary tract infections and urge incontinence. Detrusor contractions start at bladder volume of 55 ml and loss of urine is prevented by forceful pelvic floor contractions, resulting in high bladder pressures in the filling phase. During voiding bladder pressure remains normal, and after voiding there is a small after contraction. Detrusor pressure is bladder pressure minus abdominal pressure.*

cause a reflex inhibition of the contractions of the overactive detrusor muscle (fig 2). The urge to void grows stronger with the amplitude of the detrusor contraction, and in the end (with each contraction of the overactive detrusor muscle against the forcefully closed urethral sphincter) bladder pressure will rise to a high level.

In the presence of vesicoureteric reflux these high pressure waves will be transmitted to the renal pelvis and parenchyma, where they play a crucial role in the pathogenesis of reflux nephropathy—either with or without urinary tract infections.[24] The correlation between high bladder pressures and reflux nephropathy in children without anatomical or neurological obstruction of the lower urinary tract has been reported previously[8 13 14 19] and was confirmed by recent retrospective studies.[6 21]

A separate entity in children with urge syndrome is the occurrence of urethral overactivity during micturition. Urodynamically it is similar to detrusor sphincter dyssynergia[13] in neurogenic bladder dysfunction: urine flow is *staccato*, interrupted by short periods or bursts of pelvic floor activity with concomitant peaks in detrusor pressure (fig 3). Some children with urge syndrome have acquired the habit of voiding with abdominal pressure using the Valsalva manoeuvre: this too generates repeated interruptions of the urine flow through reflex triggering of pelvic floor activity by each rise in abdominal pressure. In these children, cystometric bladder capacity may reach high values and they run the risk of developing a 'lazy bladder syndrome' in spite of the fact that they initially had detrusor overactivity.

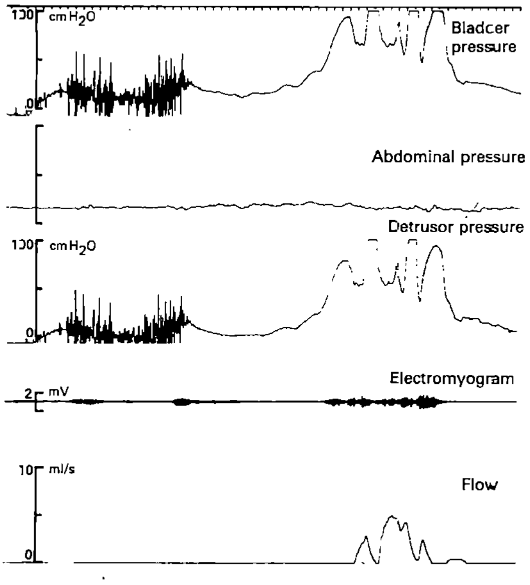

Fig 3 *'Dyssynergic' voiding: short bursts of overactivity of striated urethral and pelvic floor muscles (measured by electromyography) interrupt the flow of urine in a 7 year old girl with recurrent urinary tract infections and urge syndrome. Steep rises in bladder pressure coincide with bursts of electromyographic activity and interruptions of urine flow. Detrusor pressure is bladder pressure minus abdominal pressure.*

Treatment

Long term chemoprophylaxis has a definite place in the management of children with urge syndrome: if recurrences of urinary tract infections can be avoided for a period of six to nine months, the symptoms of imperative urge and urge incontinence will diminish appreciably—in mild cases they may even disappear. The finding of vesicoureteric reflux is of course a primary indication for long term chemoprophylaxis.

Anticholinergic drugs offer little advantage in the long run except in mild cases of the syndrome; symptoms tend to reappear immediately after discontinuation of the drugs. Anticholinergics such as oxybutynin have a more specific action on detrusor overactivity, and they seem excellently suited for a short term trial, or as an adjunct to other forms of treatment.

Muscle relaxants (for example, baclofen), or α-adrenergic blocking agents (for example, phenoxybenzamine), may have a place in the treatment of children with urge syndrome and 'dyssynergic' voiding as they lower overall urethral resistance to flow. Long term effects are less promising, however, in neurologically normal children with urge syndrome than in children with true neurogenic detrusor sphincter dyssynergia.

A more lasting effect can be expected from cognitive bladder (re)training, as many symptoms and signs of the urge syndrome are rooted in a wrong perception of signals from the bladder, and—accordingly—on habitual non-physiological responses to these signals. Children with urge syndrome have to learn again how to recognise the first sensations of urge, and how to suppress these by central inhibition instead of resorting first of all to emergency procedures like urethral compression.

They also have to learn again how to void with a completely relaxed pelvic floor. To achieve this, urodynamic signals such as urine flow rate or pelvic floor electromyogram can be used as feedback.[6 22 25–27] Feedback during training programmes has been termed 'biofeedback' by Miller: 'The use of modern instrumentation to give a person better moment-to-moment information about a specific physiological process, that is under control of the nervous system, but not clearly or accurately perceived.[28]

Since 1980 a programme for cognitive bladder training is being used at the University Children's Hospital in Utrecht,[6] with the registration of urine flow rate and voided volume serving as the feedback (fig 4). The training is organised as a 10 day course, and children are admitted to hospital where they are supervised by a psychological assistant; the same person does the pretraining interviews, supervises the course, and carries out the follow up. The children are trained in pairs; they are instructed to void at the first sensation of urge, and to use the flow recorder for every voiding. This serves to record the number of voidings each day, and the volumes voided: the number has to decrease and the volume increase. The actual flow curve, displayed directly on a monitor and printed on paper afterwards, tells the chilren how to void with a smooth uninterrupted flow: 'dyssynergic' voiding or abdominal straining show immediately, and the printout serves as proof. Medical interventions and diagnostic tests are limited to an absolute minimum during the training course, and an important part of each day is devoted to keep up with schooling.

Long term results with this programme in a group of 93 children (fig 1), all referred for long standing urge syndrome, persistent urge incontinence, and recurrent urinary tract infections, are summarised in table 2. The non-invasive flow rate recordings made during the actual training always confirmed the initial diagnosis of detrusor or urethral overactivity. In 60% of the 93 children detrusor overactivity, 'dyssynergic' voiding patterns, and concomitant urge incontinence disappeared completely without recurrences during the follow up period (3·7 (1·4) years). Nocturnal wetting, when present, also disappeared completely. In 22% of the 93 children a lasting and considerable improvement was achieved in the symptoms of the urge syndrome. Of the 18% that could not be cured, one child had structural incontinence caused by incision of the bladder neck during an earlier urethrotomy and had to be treated by colposuspension; two children had developed the 'lazy bladder syndrome' and were successfully retrained after a period of clean intermittent self catheterisation.

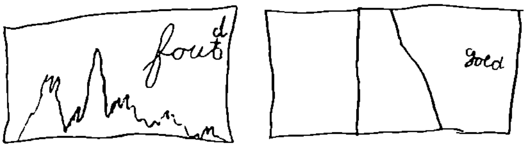

Fig 4 *Drawing by 7 year old boy of staccato urine flow (fout=wrong) and normal urine flow (goed=good). Visual perception of urine flow helps children during cognitive bladder training, and they also record the number of times they void and the amount.*

Table 2 *Association between results of cognitive bladder training and recurrences of urinary tract infections in 93 children with urge syndrome and incontinence; mean (SD) follow up 3·7 (1·4) years*

	Training results			*Total*
	Cured	*Improved*	*Relapsed*	
Urinary tract infections:				
Recurrences	4	12	15	31
No recurrences	52	8	2	62
Total	56	20	17	93

$\chi^2=46\cdot7$; df=2; $p<0\cdot001$.

In this selective group of 93 children with long standing urge syndrome, recurrent urinary tract infections had a key role, with a prevalence as high as 94%. Of the group 40% had vesicoureteric reflux, and 30% presented with signs of reflux nephropathy (table 1).

During follow up, recurrences of urinary tract infections occurred almost exclusively in conjunction with complete or partial recurrence of urge incontinence (table 2). This correlation between recurrences of urinary tract infections and urge incontinence is significant (χ^2 test, $p<0\cdot001$). Among the children that remained free of urge incontinence during follow up, there were almost no recurrences of urinary tract infections and chemoprophylaxis could safely be discontinued—often after years of recurrent urinary tract infections and persistent daytime wetting, repeated diagnostic and therapeutic procedures such as cystoscopy, urethral dilatation or urethrotomy, and numerous patient months of antibiotic and chemotherapeutic regimens. In some cases the vesicoureteric reflux disappeared.

Conclusions

Despite the fact that urge incontinence is quite different from diurnal enuresis, most children with an urge syndrome are still being labelled as having diurnal enuresis.[29] With such a label these children are bound to be referred primarily to general practice, child psychology, or even child psychiatry for diagnosis and treatment. The assocation of the urge syndrome with urinary tract infections and vesicoureteric reflux warrants a different approach, and it is worthwhile to revise the definition of diurnal enuresis accordingly: incontinence implies abnormal bladder sphincter function, enuresis denotes wetting without abnormalities of bladder sphincter function. Our results with cognitive training indicate that both detrusor overactivity and urethral overactivity are to a certain extent results of inappropriate learning processes, acutely aggravated or triggered by urinary tract infections. Prospective studies will be needed to elucidate further the exact role of urinary tract infections in the pathogenesis of the urge syndrome. The prevalence of uropathogenic *Escherichia coli* with adherence antigens in children with urge syndrome and recurrent urinary tract infections is a promising subject for research.[30] Detection of detrusor overactivity and urethral overactivity seems essential in all children with vesicoureteric reflux, because of the contribution of high bladder pressures to reflux nephropathy.[6 21–24] Much could be learned from the incorporation of bladder pressure recordings in the radiological diagnosis of vesicoureteric reflux as indicated by the lack of correlation between the grade of vesicoureteric reflux at standard cystography and the prevalence of reflux nephropathy in children with urge syndrome.

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References

[1] Lyon RP, Marshall S. Urinary tract infections and difficult urination in girls: long term follow-up. *J Urol* 1972;**105:**314–7.

[2] Van Gool JD, Tanagho EA. External sphincter activity and recurrent urinary tract infection in girls. *Urology* 1977;**10:** 348–53.

[3] Allen TD, Bright TL. Urodynamic patterns in children with dysfunctional voiding problems. *J Urol* 1978;**119:**247–9.

[4] Koff SA, Lapides J, Piazza DH. Association of urinary tract infection and reflux with uninhibited bladder contractions and voluntary sphincter obstruction. *J Urol* 1979;**122:**373–6.

[5] Hinman F Jr. Nonneurogenic neurogenic bladder (the Hinman syndrome)—15 years later. *J Urol* 1986;**136:**769–77.

[6] Van Gool JD, Kuijten RH, Donckerwolcke RA, Messer AP, Vijverberg M. Bladder-sphincter dysfunction, urinary infection and vesicoureteral reflux—with special reference to cognitive bladder training. *Contributions to Nephrology* 1984;**39:**190–210.

[7] Bauer SB, Retik AB, Colodny AH, Hallett M, Khoshbin S, Dyro FM. The unstable bladder of childhood. *Urol Clin North Am* 1980;**7:**321–36.

[8] Koff SA. Bladder-sphincter dysfunction in childhood. *Urology* 1982;**19:**457–61.

[9] Vincent SA. Postural control of urinary incontinence: the curtsey sign. *Lancet* 1966;**ii:**631–2.

[10] De Jonge GA. The urge syndrome. In: Kolvin I, McKeith RC, Meadow SR, eds. *Bladder control and enuresis*. London: Heinemann, 1973:66–9.

[11] Fielding D, Berg I, Bell S. An observational study of postures and limb movements of children who wet by day and by night. *Dev Med Child Neurol* 1978;**20:**453–61.

[12] Kondo A, Kato K, Takita T, Otani T. Holding postures characteristic of unstable bladder. *J Urol* 1985;**134:**702–4.

[13] Griffiths DJ, Scholtmeijer RJ. 'Detrusor-sphincter dyssynergia' in neurologically normal children. *Neurourology and Urodynamics* 1983;**2:**27–37.

[14] Borzyskowski M, Mundy AR. Videourodynamic assessment of diurnal urinary incontinence. *Arch Dis Child* 1987;**62:**128–31.

[15] Rees D, Whitfield HN, Islam AKMS, Doyle PT, Mayo ME, Wickham JEA. Urodynamic findings in adult females with frequency and dysuria. *Br J Urol* 1975;**47:**853–60.

[16] Kaplan WE, Firlit CR, Schoenberg HW. The female urethra syndrome: external sphincter spasm as etiology. *J Urol* 1980; **124:**48–9.

[17] Lapides J, Diokno AC. Persistence of the infant bladder as a cause for urinary infection in girls. *J Urol* 1970;**103:**243–8.

[18] Winberg J, Bergström T, Jacobsson B. Morbidity, age and sex distribution, recurrences and renal scarring in symptomatic urinary tract infection in children. *Kidney Int* 1976;**8:**S101–6.

[19] Allen TD. Vesicoureteral reflux as a manifestation of dysfunctional voiding. In: Hodson CJ, Kincaid-Smith P, eds. *Reflux nephropathy*. New York: Masson, 1979:171–81.

[20] Taylor CM, Corkery JJ, White RHR. Micturition symptoms and unstable bladder activity in girls with primary vesicoureteric reflux. *Br J Urol* 1982;**54:**494–8.

[21] Nielsen JB, Djurhuus JC, Jörgensen TM. Lower urinary tract dysfunction in vesicoureteral reflux. *Urol Int* 1984;**39:**29–31.

[22] Millard RJ, Oldenburg BF. The symptomatic, urodynamic and psychodynamic results of bladder re-education programs. *J Urol* 1983;**130:**715–9.

[23] Vincent SA. Treatment of enuresis with a perineal pressure apparatus: the irritable bladder syndrome. *Dev Med Child Neurol* 1964;**6:**23–9.

[24] Goldraich NP, Barratt TM. Vesicoureteric reflux and renal scarring. In: Holliday MA, Barratt TM, Vernier RL, eds. *Pediatric nephrology*. 2nd ed. Baltimore: Williams and Wilkins, 1987:647–66.

[25] Hellström A-L, Hjälmås K, Jodal U. Rehabilitation of dysfunctional bladder in children—method and 3-year follow up. *J Urol* 1987;**138:**847–50.

[26] Sugar EC, Firlit CF. Urodynamic biofeedback: a new therapeutic approach for childhood incontinence/infection (vesical voluntary sphincter dyssynergia). *J Urol* 1982;**128:**1253–8.

[27] Wear JB, Wear RB, Cleeland C. Biofeedback in urology using urodynamics: preliminary observations. *J Urol* 1979;**121:**464–8.

[28] Miller NE. Learning of visceral and glandular responses. *Science* 1969;**163:**434–7.

[29] Editorial. Diurnal enuresis. *Lancet* 1987;**ii:**314–5.

[30] Kallenius G, Winberg J. Bacterial adherence to periurethral epithelial cells in girls prone to urinary tract infections. *Lancet* 1978;**ii:**540–2.

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Current topic

Endocrine consequences of treatment of malignant disease

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Cancer is a major cause of morbidity and mortality in childhood and affects about one in 650 children by the age of 15 years. When survival during the three decades 1954–63, 1964–73, and 1974–83 was compared striking improvements were observed.[1] For all childhood cancers, five year survival increased from 21% in the first decade to 49% in the third decade. During the first and third decades five year survival rates for acute lymphoblastic leukaemia increased from 2% to 47%, for Hodgkin's disease from 44% to 91%, for Wilms' tumour from 31% to 85%, and for medulloblastoma from 25% to 41%.

The improved chances of survival have stimulated great interest in the effects on the endocrine system and the impairment of growth after radiotherapy and cytotoxic chemotherapy for childhood cancer.

Radiation may directly impair hypothalamic, pituitary, thyroid, and gonadal function, or alternatively it may induce the development of hyperparathyroidism, thyroid adenomas, or carcinomas. Cytotoxic chemotherapy may damage the gonad and both irradiation and cytotoxic chemotherapy may interfere with the normal growth of bone. These complications of treatment may lead to various clinical presentations including short stature, failure to undergo normal pubertal development, precocious puberty, hypothyroidism, thyroid tumours, hyperparathyroidism, gynaecomastia, and varying degrees of hypopituitarism.

Brain tumours

GROWTH

Short stature is a common complication after the treatment of brain tumours in childhood. These brain tumours include gliomas, ependymomas, and medulloblastomas—all lesions that do not directly affect the hypothalamic-pituitary axis. The treatment of these tumours may include operation, cranial or craniospinal irradiation, and chemotherapy. The final height achieved by the patients may be adversely influenced by a number of factors including growth hormone deficiency, impaired spinal growth, precocious puberty, chemotherapy, malnutrition, and occult tumour.

The impact of malnutrition and residual tumour on growth has not been studied in these children and there are few studies of cytotoxic chemotherapy and growth retardation.

GROWTH HORMONE DEFICIENCY

Irradiation of the hypothalamic-pituitary axis may produce a range of pituitary hormone deficiencies ranging from isolated growth hormone deficiency to panhypopituitarism.[2] Of the six anterior pituitary hormones, the first to be affected by radiation damage is always growth hormone, followed by gonadotrophin and adrenocorticotrophic hormone secretion. The extent of hypothalamic-pituitary dysfunction is dose dependent, growth hormone deficiency occurring at lower doses of irradiation, and panhypopituitarism after higher doses. The speed with which individual pituitary hormone deficiencies occur is also dose dependent. The higher the radiation dose, the earlier growth hormone deficiency will develop after treatment. In children irradiated for a brain tumour, a radiation dose to the hypothalamic-pituitary axis of between 2700 and 3500 cGy over three weeks is sufficient to produce subnormal growth hormone responses to standard provocation tests in most patients within two years of radiotherapy. In an occasional patient, however, growth hormone deficiency may not occur for three to six years after irradiation.

Both the hypothalamus and the pituitary may be directly damaged by irradiation. There are a number of studies, however, which indicate that the hypothalamus is more vulnerable to such damage than the pituitary. Therefore the primary pathophysiological defect in such children is likely to be subnormal endogenous production of growth hormone releasing hormone rather than inadequate growth hormone secretion by pituitary somatotrophs. Thus if an intranasal or depot preparation of a suitable growth hormone releasing hormone analogue becomes available, it may prove ideal for the treatment of children with radiation induced growth hormone deficiency.

SPINAL IRRADIATION AND GROWTH

Children treated for medulloblastomas, ependymomas, and certain other brain tumours receive spinal as well as cranial irradiation. After a dose of spinal irradiation of 2700 to 3500 cGy over 22 to 27 days spinal growth may be appreciably impaired.[3] The younger the child at the time of irradiation, the greater the loss in growth potential—from 9 cm if irradiated at 1 year of age, to 5·5 cm at 10 years of age. It is likely that these estimates of eventual loss in height are conservative figures and furthermore, in centres where the spinal irradiation dose is greater than that used in the above study, even more potential growth may be lost. Much of the impairment in spinal growth occurs during puberty, irrespective of the age at irradiation. Consequently, the prognosis for spinal growth in an irradiated child who is still prepubertal should not be too optimistic.

PRECOCIOUS PUBERTY

Early[4] or precocious[5] puberty has been reported in some children who have received cranial irradiation. The onset of puberty at a very young age is, however, rarely seen. Puberty starts at appreciably earlier chronological and bone ages in children with radiation induced growth hormone deficiency compared with children who have idiopathic growth hormone deficiency.[2] The radiation induced shift in the onset of puberty may affect both sexes. The clinical implication for the treatment of children with radiation induced growth hormone deficiency and early puberty is to foreshorten the time available for treatment with growth hormone.

TREATMENT WITH GROWTH HORMONE

Data about final height in children with radiation induced growth hormone deficiency after the treatment of brain tumours indicate that their growth in response to treatment is less impressive than that seen in children with idiopathic growth hormone deficiency. I have already discussed some of the factors such as spinal irradiation and early puberty which prevent a better growth response. None the less, in the group with cranial irradiation alone, treatment with growth hormone prevented further loss in height SD scores,[6] while in the children who received craniospinal irradiation growth hormone restricted the amount of further loss in height SD scores.[7]

A further important adverse factor in the height prognosis of these children was the time interval between irradiation and initiation of treatment with growth hormone, which averaged between 5·5 and 6·7 years.[6 7] There is little doubt that better results would have been achieved if treatment with growth hormone had been started earlier. This leads on to the fundamental question of when should treatment with growth hormone be started?

There has been a tendency to wait until the child exhibits a poor growth rate. Adverse factors, however, such as impaired spinal growth and cytotoxic chemotherapy, may lead to poor growth and—alternatively—early puberty may be associated with an 'apparently normal' growth rate that may give rise to false optimism about the child's height prognosis.

What, if any, tests of growth hormone secretion should be carried out? Lannering and Albertsson-Wiklund suggested that 24 hour spontaneous growth hormone profiles provide the most useful information.[8] For pragmatic reasons, however, I believe that the 24 hour growth hormone profile is likely to remain a research investigation, as the demands on the laboratory and clinical team make it unacceptable as a routine method of investigation in paediatric endocrinology. Furthermore, discordancy between physiological growth hormone secretion and growth hormone responses to pharmacological stimuli is uncommon after the higher doses of cranial irradiation used in the treatment of brain tumours. The majority of such children will therefore show a subnormal growth hormone response to an insulin tolerance test as well as blunted physiological growth hormone secretion. If tests of growth hormone secretion are carried out, the insulin tolerance test remains a particularly useful investigation in the child who has received cranial irradiation.

The chances of recurrence of a brain tumour are greatest within two years of the primary treatment of the tumour.[2] There is no evidence that treatment with growth hormone increases the risk of recurrence of a brain tumour in children with radiation induced growth hormone deficiency.[9] One reasonable approach therefore would be to treat all the children with brain tumours treated by standard radiation schedules (including a dose to the hypothalamic-pituitary axis in excess of 2700 cGy) with growth hormone two years after their primary treatment. At this time they would no longer be receiving cytotoxic chemotherapy, the chance of recurrence of a tumour is low, and it is established that most will be growth hormone deficient by this time. This policy would not require routine tests of growth hormone secretion. One drawback, however, is that a minority of the children would receive growth hormone at a time when they had not yet developed growth hormone deficiency.

In practice, I submit the children at our own centre to routine annual insulin tolerance test and arginine stimulation test from two years after irradiation until the decision is taken to start them on treatment with growth hormone. Other centres may choose different provocation tests and at least one centre does not carry out any tests at all, but treats all children irradiated for brain tumours with growth hormone two years after irradiation. Whatever policy an individual centre practices, the principle of administering treatment with growth hormone earlier in this group of children is central to the prognosis of their ultimate height.

THYROID DYSFUNCTION

Direct irradiation to the thyroid gland is a consequence of the spinal component of craniospinal irradiation. The two serious complications of radiation induced thyroid damage are hypothyroidism and thyroid tumours.[10]

Hyperparathyroidism may develop many years after neck irradiation in adults and, despite the fact that this specific complication has not been described after irradiation in children, it is clearly a possibility.

Radiation induced thyroid tumours may be benign or malignant. Typically there is a long latency period between irradiation and the clinical presentation with a thyroid swelling. In clinical practice any children who have received neck irradiation should have their thyroid glands palpated at least once a year. Routine use of isotope scanning is not recommended.

The degree of thyroid dysfunction after thyroid irradiation may range from frank hypothyroidism with increased concentration of thyroid stimulating hormone and low thyroxine concentration, to subtle disturbance with increased thyroid stimulating hormone, and normal thyroxine concentrations. A thyrotrophin releasing hormone test is unnecessary. An annual assessment of the basal thyroid stimulating hormone and thyroxine concentrations will suffice in children who have been irradiated.

In children with obvious biochemical hypothyroidism, thyroxine replacement is indicated. If the only abnormality in the thyroid function tests is an increase in the concentration of thyroid stimulating hormone, then interpretations in reports about adult patients vary between mild hypothyroidism and 'compensated thyroid dysfunction'. In the context of children who have been irradiated, this is an academic discussion as treatment with thyroxine is indicated for a number of reasons. Firstly, there is strong circumstantial evidence that an increased concentration of thyroid stimulating hormone may increase the risk of thyroid tumours developing in an irradiated thyroid gland. Secondly, in a child who may be short for a number of reasons it is important to be certain that the child is euthyroid. These arguments weigh strongly in favour of early thyroxine replacement with a dose of thyroxine sufficient to restore the circulating concentration of thyroid stimulating hormone to within the normal range.

There is one report that suggests that the incidence of thyroid dysfunction is significantly greater in children who receive cytotoxic chemotherapy and craniospinal irradiation compared with craniospinal irradiation alone.[11] I know of no conclusive evidence, however, that cytotoxic chemotherapy alone may modify thyroid function.

GONADAL DYSFUNCTION

Both the adjuvant cytotoxic chemotherapy and the spinal fields of irradiation may damage the gonads in children treated for brain tumours. Long term follow up in 21 girls and 29 boys who had received a nitrosourea—carmustine (BCNU) or lomustine (CCNU)—with or without procarbazine has shown that there is a high incidence of primary gonadal dysfunction.[12 13] Both sexes progressed through puberty normally with consistently raised basal concentrations of follicle stimulating hormone and occasionally increased concentrations of luteinising hormone. The girls achieved menarche at an appropriate age. As adults most of the boys had inappropriately small testicular volumes, which are likely to be associated with severe oligospermia or azoospermia, and infertility. In these children, as in those treated for other malignant diseases, gonadal damage in prepubertal life may not be associated with abnormal gonadotrophin concentrations either basally or after gondatrophin releasing hormone stimulation; these develop during the peripubertal years.

A sex difference in the reversibility of damage was observed. The boys showed no evidence of recovery of germinal epithelial function and no deterioration in Leydig cell function in a follow up extended to 11 years. In contrast, several girls who had previously been shown to have ovarian damage have continued with regular menses and normal follicle stimulating hormone and oestradiol concentrations. Although it was not known whether these cycles were ovulatory, it is likely that these girls had recovered from the ovarian damage. The prospects for fertility among such girls are good in the early child bearing years.

As with other cytotoxic combinations, however, premature menopause remains a possibility.

Many of these children have also received craniospinal irradiation, which results in scattered doses to the gonad. In the boys, this results in a small total dose to the testis (estimated at 46–120 cGy after a fractionated course of total spinal dose 3500 cGy in the Manchester centre). This is likely to contribute to testicular damage, as seen in individual boys treated with craniospinal irradiation but no chemotherapy who have developed testicular dysfunction.[14] In girls, however, the dose of irradiation to the ovary may show greater variation. In the Manchester centre a total dose in the range 90–1000 cGy has been estimated to reach the ovary; this may contribute appreciably to ovarian dysfunction, which may be irreversible. The scattered dose to the ovary will differ among treatment centres depending on the method of giving the radiotherapy. Hence the individual contributions of spinal irradiation and cytotoxic chemotherapy to ovarian damage will vary.[15]

Acute lymphoblastic leukaemia

GROWTH

Much confusion and controversy have been generated over the growth patterns and growth hormone requirements of the child with acute lymphoblastic leukaemia treated with prophylactic cranial irradiation and combination cytotoxic chemotherapy for several years. Some groups have found no adverse effect on final height, while other groups (including our own) have noted a modest adverse effect on growth,[16] but as final height is unknown in most of the children, the possibility of impaired pubertal growth may mean that final height loss is substantial in a proportion of children. Finally, there is a third group,[17] who have studied children with acute lymphoblastic leukaemia and found a much greater retardation of growth. An analysis of the radiation schedules and chemotherapy protocols used in the different centres has led to some understanding of the explanation for the differences in height loss observed between groups.

There is in vitro evidence that cytotoxic chemotherapy may effect growth mechanisms and in vivo evidence of an effect on growth.[16 17] In the child with acute lymphoblastic leukaemia the duration and nature of the combination cytotoxic chemotherapy will influence the growth prognosis. After treatment with regimens used in the United Kingdom the effects of cytotoxic chemotherapy are likely to be minor, but more intense cytotoxic chemotherapy regimens have had a profound impact on growth.

Children irradiated prophylactically for acute lymphoblastic leukaemia rather than for a brain tumour tend to receive a lower radiation dose to the hypothalamic-pituitary axis. Most of the growth studies have been carried out in children who received a total cranial radiation dose of 2400–2500 cGy. The incidence of growth hormone deficiency in such children will depend on the number of fractions, fraction size, and duration of the radiation schedule.

For a number of reasons the demand for treatment with growth hormone is more difficult to predict after treatment for acute lymphoblastic leukaemia than after a brain tumour. I have already discussed the dissimilar growth patterns in children with acute lymphoblastic leukaemia studied by different groups. In the children with severe growth retardation, even though cytotoxic chemotherapy is a serious adverse factor, radiation induced growth hormone deficiency is common.[17] It is appropriate therefore that most of these children are offered treatment with growth hormone whereas I have only treated a minority of the children with acute lymphoblastic leukaemia in Manchester.[16] The clinical dilemma is how to identify the few who should receive treatment. We have suggested that those children who are below the tenth centile or whose growth rate is persistently poor after completion of cytotoxic chemotherapy, and who have growth hormone deficiency, should receive a therapeutic trial of growth hormone.[16] It should be understood, however, that this is an arbitrary definition of growth hormone requirement.

Moëll *et al* have studied the growth patterns of children with acute lymphoblastic leukaemia during different phases of childhood.[18] Their girls treated for acute lymphoblastic leukaemia lost very little standing height SD score during prepubertal life, as in other studies, but had an attenuated pubertal growth spurt. The contribution of growth hormone deficiency to the disturbed pubertal growth and the effect of treatment with growth hormone to improve it, with or without the addition of a gonadotrophin releasing hormone analogue to delay the rather early pubertal onset in some of the girls, are under investigation.[19]

Since 1980 the total dose of cranial irradiation for acute lymphoblastic leukaemia has been reduced to 1800 cGy. There are, however, few detailed studies of growth hormone secretion after this dose and the growth data available cover only the first four to five years after irradiation.[2]

THYROID DYSFUNCTION

In the past the prophylactic irradiation of the central nervous system for acute lymphoblastic leukaemia included spinal as well as cranial fields. The possibility of radiation induced thyroid tumours or thyroid dysfunction, therefore, exists as previously discussed. In recent years children with acute lymphoblastic leukaemia have not received spinal irradiation, and so thyroid damage should not occur.

GONADAL DYSFUNCTION

The impact, both transient and permanent, of combination cytotoxic chemotherapy on gonadal function is totally dependent on the nature and dosage of the drugs received by the child.

In boys who received cyclophosphamide or cytosine arabinoside, or both, as part of their combination cytotoxic chemotherapy for acute lymphoblastic leukaemia, the germinal epithelial morphology was profoundly disturbed.[20] In others who did not receive alkylating drugs or methylhydrazines, the gonadotrophin and testosterone concentrations, and semen analysis, were normal. Lendon *et al* had indicated that the damage to the testicular germinal epithelium was likely to be reversible and therefore fertility a realistic prospect.[20]

In girls the outlook is even brighter, in that cytotoxic chemotherapy induced ovarian damage has been reported only rarely. Morphological studies have shown that the main abnormality is inhibition of follicular maturation rather than severe depletion of primordial follicles, an observation more consistent with reversible rather than with permanent functional changes.[21] Both boys and girls progress through puberty spontaneously indicating that gonadal steroidogenesis is adequate.

Most boys with leukaemic relapse of the testes receive direct testicular irradiation with a total dose between 2000 and 2400 cGy. The effects of the testicular irradiation are dependent on the age and pubertal stage of the boy.[22-24] The young prepubertal boy seems most vulnerable to the development of severe and persistent testicular dysfunction. The germinal epithelium is completely ablated in all, and Leydig cell function seriously affected in most. Increased basal concentrations of follicle stimulating hormone and luteinsing hormone will often first occur around the ages of 9 to 10 years. The serum testosterone concentration is usually low, which is of course normal for a prepubertal boy, but there is an inadequate or absent testosterone response to an acute bolus of human chorionic gonadotrophin. Most boys require androgen replacement to enable normal pubertal development to occur. Initiation of androgen replacement should be considered around 12 to 13 years of age, and the requirement will be permanent.

Girls are also susceptible to radiation induced gonadal damage during treatment of acute lymphoblastic leukaemia.[25] In 97 girls treated for acute lymphoblastic leukaemia with identical regimens of cytotoxic chemotherapy but different modalities of irradiation, abnormalities of follicle stimulating hormone or luteinising hormone secretion, or both, were more commonly seen after craniospinal combined with abdominal irradiation, than after craniospinal irradiation alone. Not surprisingly, abnormalities of gonadotrophin secretion were rare in the group that received cranial irradiation alone. After craniospinal and abdominal irradiation, arrested puberty and delayed menarche occurred because of the ovarian damage.

Bone marrow transplantation

Marrow transplantation has become a life saving procedure for an increasing number of children and young adults with either non-malignant or malignant haematological disorders, in particular leukaemia. Follow up studies evaluating growth and development have shown that the delayed effects are related to the regimen used for preparation for marrow transplantation. Few endocrine abnormalities have been observed after regimens containing only high doses of cyclophosphamide, but growth disturbance and multiple endocrine abnormalities have been seen after regimens that include total body irradiation.[26]

Total body irradiation has been given in single dose exposures of 750 to 1000 cGy, and more recently in fractionated exposures of total doses ranging from 1200 to 1575 cGy given over three to seven days. In a series of 116 children who received transplants for malignancy after preparation with cyclophosphamide and total body irradiation, 18% developed compensated thyroid dysfunction, 11% developed hypothyroidism and two children developed thyroid tumours four and eight years later.[26]

As might be expected, there is a high incidence of gonadal dysfunction after total body irradiation with ablation of the germinal epithelium in the boys and irreversible ovarian failure in most of the girls. The degree of Leydig cell failure is dependent on the pubertal stage of the boy, and whether or not he has received previous testicular irradiation.

Severe growth disturbance is common and may be caused by various aetiological factors including growth hormone deficiency, thyroid dysfunction, radiation induced impairment of bone growth, or graft versus host disease and its treatment. Growth hormone deficiency may occur even if the child has not previously received prophylactic cranial irradiation.[27] It is, however, too early to draw conclusions about the beneficial effects of treatment with growth hormone in growth hormone deficient children after total body irradiation, but there is room for optimism.

Abdominal tumours

In the past it was more common to find that children with malignancies such as Wilms' tumour received whole abdomen irradiation. Gonadal dysfunction was common, with azoospermia and infertility resulting from the scatter dose of irradiation to the testes, and ovarian failure caused by direct radiation damage to the ovaries. In the girls in whom ovarian function was preserved the reproductive outcome was still poor, presumably as a result of the effects of irradiation on the uterus or its blood supply.[28]

Fortunately irradiation of the whole abdomen for Wilms' tumour is used much less often now. If radiotherapy is given then only the relevant flank is treated. Consequently the incidence of ovarian failure and azoospermia have been dramatically reduced.

Irradiation, both of the whole abdomen and of the flank, will include part of the vertebral column in the radiation field. Some degree of skeletal disproportion and height loss will therefore occur, but this is less than that seen after irradiation of the whole spine for brain tumours.

Lymphomas

Hypothyroidism, compensated thyroid dysfunction, and thyroid tumours may occur in children who have received neck or mediastinal irradiation for lymphoma.

In those boys treated with six or more courses of MVPP (mustine, vinblastine, procarbazine, and prednisolone) or MOPP (mustine, vincristine, procarbazine, and prednisolone) testicular dysfunction is inevitable.[29] The damage to the germinal epithelium is severe and seems irreversible, whereas Leydig cell dysfunction—if it occurs—is subtle and does not prevent the boys from progressing through puberty spontaneously.

Gonadal dysfunction is less common in girls than in boys but it may occur and, if so, then sex steroid replacement may be necessary for pubertal development. It is likely but not proved that ovarian function is less vulnerable to cytotoxic chemotherapy induced damaged in young girls than in adult women in whom the incidence of ovarian failure is between 15 and 60%.

Conclusions

In this review I have concentrated on the growth and endocrine results of the treatment of the more common childhood malignancies. Irrespective of the primary malignancy, however, the damage is caused if the radiation field includes an endocrine gland, or if a cytotoxic chemotherapy regimen contains gonadotoxic drugs. For instance, if a child is growing poorly after irradiation for a rhabdomyosarcoma of the orbit, consider the possibility that an appreciable amount of irradiation reached the hypothalamic-pituitary axis and caused growth hormone deficiency. Alternatively, if a boy has received combination cytotoxic chemotherapy for a bone tumour and has pathologically small testes, consider the possibility that the alkylating agent or cisplatinum used in the cytotoxic chemotherapy regimen has caused severe damage to the germinal epithelium. The first boy may require treatment with growth hormone, while the second will need some advice and counselling about his potential infertility at the appropriate time.

All children attending an oncology centre should have their standing height, weight, and pubertal stage noted at each visit. The measurements should be recorded on standard Tanner growth charts. If all or part of the child's spine has been irradiated then the sitting height should be measured regularly. There are standard charts available for recording growth in leg length and sitting height.

The oncologist can screen for abnormalities of thyroid function and morphology, and many oncologists will feel competent to titrate the replacement dose of thyroxine against the clinical state, and thyroid stimulating hormone and thyroxine concentrations of the child.

Growth disturbance and the hormonal management of pubertal development are much more complicated and require expertise in endocrinology. The equipment required consists of standing and sitting height stadiometers and an orchidometer. The personnel must include an endocrinologist and an oncologist.

The numbers of patients recovering from cancer in childhood are growing, and for optimum management every major paediatric oncology service should offer a combined clinic at which both the paediatric oncologist and the endocrinologist contribute.

References

[1] Birch JM, Marsden HB, Morris-Jones PH, Pearson D, Blair V. Improvements in survival from childhood cancer: results of a population based survey over 30 years. *Br Med J* 1988;**296:** 1372–6.

[2] Shalet SM, Clayton PE, Price DA. Growth and pituitary function in children treated for brain tumours or acute lymphoblastic leukaemia. *Horm Res* 1988;**30:**53–61.

[3] Shalet SM, Gibson B, Swindell R, Pearson D. Effect of spinal irradiation on growth. *Arch Dis Child* 1987;**62**:461–4.

[4] Winter RJ, Green OC. Irradiation-induced growth hormone deficiency, blunted growth response and accelerated skeletal maturation to growth hormone therapy. *J Pediatr* 1985;**106**: 609–12.

[5] Brauner R, Czernichow P, Rappaport R. Precocious puberty after hypothalamic and pituitary irradiation in young children. *N Engl J Med* 1984;**311**:920.

[6] Clayton PE, Shalet SM, Price DA. Growth response to growth hormone therapy following cranial irradiation. *Eur J Pediatr* 1988;**147**:593–6.

[7] Clayton PE, Shalet SM, Price DA. Growth response to growth hormone therapy following craniospinal irradiation. *Eur J Pediatr* 1988;**147**:597–601.

[8] Lannering B, Albertsson-Wiklund K. Growth hormone release in children after cranial irradiation. *Horm Res* 1987;**27**:13–22.

[9] Clayton PE, Shalet SM, Gattamaneni HR, Price DA. Does growth hormone cause relapse of brain tumours? *Lancet* 1987;**i**:711–3.

[10] Barnes ND. Effects of external irradiation on the thyroid gland in childhood. *Horm Res* 1988;**30**:84–9.

[11] Livesey EA, Brook CGD. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours. *Arch Dis Child* 1989;**64**:593–5.

[12] Clayton PE, Shalet SM, Price DA, Morris-Jones PH. Testicular damage after chemotherapy for childhood brain tumours. *J Pediatr* 1988;**112**:922–6.

[13] Clayton PE, Shalet SM, Price DA, Morris-Jones PH. Ovarian function following chemotherapy for childhood brain tumours. *Med Pediatr Oncol* 1989;**17**:92–6.

[14] Brown IM, Lee TJ, Eden OB, Bullimore JA, Savage DCL. Growth and endocrine function after treatment for medulloblastoma. *Arch Dis Child* 1984;**58**:722–7.

[15] Livesey EA, Brook CGD. Gonadal dysfunction after treatment of intracranial tumours. *Arch Dis Child* 1988;**63**:495–500.

[16] Clayton PE, Shalet SM, Morris-Jones PH, Price DA. Growth in children treated for acute lymphoblastic leukaemia. *Lancet* 1988;**i**:460–2.

[17] Kirk JA, Raghupathy P, Stevens MM, *et al.* Growth failure and growth hormone deficiency after treatment for acute lymphoblastic leukaemia. *Lancet* 1987;**i**:190–3.

[18] Moell C, Garwicz S, Westgren U, Wiebe T. Disturbed pubertal growth in girls treated for acute lymphoblastic leukaemia. *Pediatric Hematology and Oncology* 1987;**4**:1–5.

[19] Leiper AD, Stanhope R, Preece MA, Grant DB, Chessells JM. Precocious or early puberty and growth failure in girls treated for acute lymphoblastic leukaemia. *Horm Res* 1988;**30**:72–6.

[20] Lendon M, Hann IM, Palmer MK, Shalet SM, Morris-Jones PH. Testicular histology after combination chemotherapy in childhood for acute lymphoblastic leukaemia. *Lancet* 1978;**ii**:439–41.

[21] Himmelstein-Braw R, Peters H, Faber M. Morphological study of the ovaries of leukaemic children. *Br J Cancer* 1978;**38**:82–7.

[22] Shalet SM, Horner A, Ahmed SR, Morris-Jones PH. Leydig cell damage after testicular irradiation for lymphoblastic leukaemia. *Med Pediatr Oncol* 1985;**13**:65–8.

[23] Leiper AD, Grant DB, Chessells JM. Gonadal function after testicular radiation for acute lymphoblastic leukaemia. *Arch Dis Child* 1986;**61**:53–6.

[24] Brauner R, Caltabiano P, Rappaport R, Leverger G, Schaison G. Leydig cell insufficiency after testicular irradiation for acute lymphoblastic leukaemia. *Horm Res* 1988;**30**:111–4.

[25] Hamre MR, Robison LL, Nesbit ME, *et al.* Effects of radiation on ovarian function in long-term survivors of childhood acute lymphoblastic leukaemia: a report from the children's cancer study group. *J Clin Oncol* 1987;**5**:1759–65.

[26] Sanders JE, Buckner CD, Sullivan KM, *et al.* Growth and development in children after bone marrow transplantation. *Horm Res* 1988;**30**:92–7.

[27] Borgstrom B, Bolme P. Growth and growth hormone in children after bone marrow transplantation. *Horm Res* 1988;**30**:98–100.

[28] Li FP, Gimbrere K, Gelber RD, *et al.* Outcome of pregnancy in survivors of Wilms' tumour. *JAMA* 1987;**257**:216–9.

[29] Whitehead E, Shalet SM, Morris-Jones PH, Beardwell CG, Deakin DP. Gondal function after combination chemotherapy for Hodgkin's disease in childhood. *Arch Dis Child* 1982;**57**:289–91.

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Archives of Disease in Childhood, 1989, **64,** 1642–1644

Correspondence

Rewarming infants on a heated mattress

Sir,

Sarman *et al* have shown that a heated, water filled mattress can provide a superior alternative to maternal skin contact, or an incubator, for rapidly attaining and maintaining normal body temperature in the low birthweight neonate.[1] In this country, where power failures are very infrequent, an electric mattress heater may be as useful and simple a means of ensuring rapid restoration of normal temperature in the newborn.

To test the effect of such a heater I measured the rectal temperatures of 38 full term infants delivered by uncomplicated vaginal delivery in cephalic presentation after labours lasting no longer than 10 hours. Two groups of infants were studied: 20 born of mothers who had received 100–150 mg pethidine during the last six hours of labour (mean birth weight 3315 g), and 18 who had not (mean birth weight 3339 g). Half of these two groups of infants was nursed in a cot with a 40 watt electric heating pad (Thermega) beneath the mattress, and half was not.

All infants were dried and wrapped in two towels immediately after delivery before transfer to the postnatal ward where their rectal temperatures were recorded with a mercury thermometer. No toilet was performed but a rectal thermocouple (Light Laboratories) was inserted to 3 cm before infants were rewrapped and left undisturbed for the next four hours in a cot in a side room with an ambient temperature of 26°C. Rectal temperatures were recorded at 1, 2, 3, and 4 hours of age. At 4 hours the rectal thermocouple was removed and the infants received their first toilet. Thereafter, until 24 hours, when the rectal temperature was recorded with a mercury thermometer, all infants were nursed without the heating pad.

The rate of rise of the mean rectal temperature of those infants nursed in cots with a heating pad beneath their mattress was faster than that of infants nursed without, whether or not their mothers had received pethidine ($p<0\cdot01$) (figure). At four and 24 hours there was no significant difference between the mean temperatures of the four groups of infants. The temperature recorded between the upper surface of the mattress and the wrapped infant in a cot containing a heater was 33·4°C and that without a heater 34·8°C.

This small study shows that an electric undermattress heating pad rapidly restores body temperature to normal in the healthy neonate, whether or not he or she has been exposed to pethidine in utero. Such a heating pad is safe and effective and may obviate the use of a radiant heater to diminish loss of body heat from non-asphyxiated infants born of mothers who have received pethidine in labour.[2–4] After prompt drying at birth infants may be safely left wrapped and undisturbed until first toilet at 4 hours of age.

Such an electric undermattress heater may well prove equally effective in the management of the low birthweight newborn who does not require nursing in an incubator.

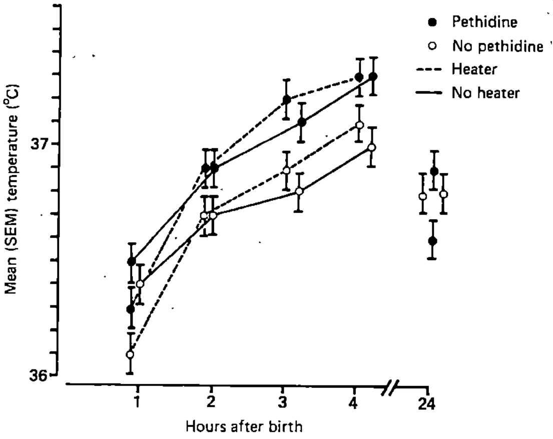

Figure . *Rectal temperatures of neonates nursed in a cot with and without a heated mattress.*

I should like to thank Dr EN Hey and the midwives of the Princess Mary Maternity Hospital for their help with this study.

References

[1] Sarman I, Can G, Tunell R. Rewarming preterm infants on a heated, water filled mattress. *Arch Dis Child* 1989;**64**:687–92.

[2] Burnard ED, Cross KW. Rectal temperature in the newborn infant after birth asphyxia. *Br Med J* 1958;**ii**:1197–9.

[3] Dahm LS, James LS. Newborn temperature and calculated heat loss in the delivery room. *Pediatrics* 1972;**49**:504–13.

[4] Smales ORC, Kime R. Thermoregulation in babies immediately after birth. *Arch Dis Child* 1978;**53**:58–61.

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Cholesterol and diet

Sir,

Dr Tarlow reports that the fat intake of many British children currently exceeds 50% of the total energy of the diet.[1]

The target he sets is 35% of total energy without prejudicing growth or producing an unpleasant diet. Your readers might be interested in some preliminary findings of dietary intake at 18 months in a sample of 170 Hong Kong Chinese infants who are participating in a longitudinal study of growth and nutritional inter-relationships from birth to 5 years.

Fat contributed about 30% of total daily energy consumption at 18 months. Most infants were then eating a diet of rice, fish, meat, and vegetables. Butter and high fat desserts were rarely given and ice cream only occasionally consumed. Energy intake was 0·414 MJ/kg/day, very similar to energy intake in recent studies from Canadian[2] (0·401 MJ) and Australian[3] children (0·418 MJ) of the same age. Our infants enjoyed excellent health and were growing and developing normally.

In Hong Kong even with its obvious western influences the traditional Chinese diet in early childhood is low in total fat and cholesterol and saturated fats. As children grow older, however, the situation is likely to change as ubiquitous 'fast foods' increase their stranglehold on children's diets. It remains to be seen whether the very low fat intake of the early years in any way influences health in the long term especially in relation to cardiovascular diseases.

References

[1] Tarlow MJ. Cholesterol and diet. *Arch Dis Child* 1989;**64**: 647–8.

[2] Yeung DL. *Infant nutrition. A study of feeding practices and growth from birth to 18 months*. Ottawa, Canada: The Canadian Public Health Association, 1983.

[3] Hitchcock NE, Gracey M, Gilmour AI, Owles EN. Nutrition and growth in infancy and early childhood. A longitudinal study from birth to five years. *Monographs in paediatrics 19*. Basel: Karger, 1986.

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Educating medical students about death and dying

Sir,

I read with interest the article by Black *et al*, which points out the need to address the stressful feelings medical students and physicians have about dying and death.[1] The authors propose a course with objectives varying from identifying the dying patients' and family needs and their dealing with grief, to clearing away barriers set up by physicians surrounding death. A course of this type would no doubt improve a physician's ability to deal with death and dying, and would be helpful to their dying patients and their families. However, I feel the course proposed lacks one more important objective: obtaining permission for a necropsy and feedback to the family about the necropsy findings.

The information gained from a necropsy, and properly presented to the family, may relieve the guilt that is a consequence of most deaths, provides assurance that the patient received proper medical care, and facilitates the grieving process.[2–4] As Hill and Anderson point out, the necropsy not only gives the physician the benefit of learning from his or her own experience, but also enables the medical student to accept the fact of death as an inescapable part of caring for the sick.[4]

References

[1] Black D, Hardoff D, Nelki J. Educating medical students about death and dying. *Arch Dis Child* 1989;**64**:750–3.

[2] Valdes-Dapena MA. The pathologist's conference with patients following post mortem examination of their child: an application of the Kubler-Ross concept. *Perspect Pediatric Pathol* 1979;**5**:263–7.

[3] Favara BE, Cotteau C, McIntyre L, Valdes-Dapena M. Pediatric pathology and the autopsy. *Pediatr Pathol* 1989;**9**:19–116.

[4] Hill RB, Anderson RE. *The autopsy—medical practice and public policy*. Massachusetts: Butterworth, 1988:127.

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Rise in urea concentration after arginine hydrochloride infusion

Sir,

In order to test the renal ability of children to acidify their urine, an adequate degree of metabolic acidosis is usually obtained either by the oral administration of ammonium chloride or by the infusion of arginine hydrochloride.[1] The intravenous infusion of arginine hydrochloride—which is used also to study growth hormone, glucagon, and insulin release[2 3]—has been described as safe and free of immediate or delayed untoward effects. Transient renal dysfunction, hypophosphataemia, and hyperkalaemia have, however, been described after arginine administration to normal subjects.[4]

When reviewing arginine acidification tests performed in our clinic, we observed a significant progressive increase in plasma urea concentrations in children with normal glomerular filtration rate undergoing the test. In seven children aged 5 months to 6 years, the intravenous administration of arginine hydrochloride (100–150 mmol/m^2 over 120–150 minutes) increased mean (SD) plasma urea from 5·1 (0·5) to 7·3 (0·6) mmol/l at 60 minutes ($p<0·001$)

and to 9·5 (0·8) mmol/l at 120 minutes ($p<0·001$) after starting the infusion of arginine hydrochloride.

The observed increase in plasma urea is likely to be due to the cleavage of L-arginine to urea and ornithine catalysed in the liver by the enzyme L-arginase. This enzyme is present in the liver of all ureotelic organisms and, like most mammalian enzymes, only acts on the L-isomer. To test this hypothesis, we measured the changes in plasma urea concentrations occurring in eight anaesthetised and mechanically ventilated rabbits infused with either L-arginine or D-arginine at doses comparable with those used during an acidification test. After the infusion of L-arginine (0·05 mmol/kg/minute) in three animals, mean (SD) plasma urea rose from 6·4 (2·1) to 7·6 (2·1) mmol/l at 60 minutes ($p<0·01$) and to 8·9 (2·2) mmol/l at 120 minutes ($p<0·01$). By contrast, the infusion of the same dose of the D-isomer in three other rabbits did not significantly modify plasma urea (5·9 (0·2) before the infusion, 6·0 (0·1) at 60 minutes and 6·5 (0·1) mmol/l at 120 minutes). Plasma urea also remained stable in the two saline infused control rabbits.

Our clinical and experimental data thus suggest that cleavage of L-arginine to urea and ornithine by the liver L-arginase is probably responsible for the increase in plasma urea concentrations observed in children infused with arginine hydrochloride. The lack of endogenous D-arginase explains the failure of urea to increase after the administration of D-arginine. While this rise of plasma urea does not have any deleterious effects in children with normal renal function, it may likely lead to misinterpretation of urea data collected during an arginine infusion test.

References

[1] Loney LC, Norling LL, Robson AM. The use of arginine hydrochloride infusion to assess urinary acidification. *J Pediatr* 1982;**100**:95–8.

[2] Parker ML, Hammond JM, Daughaday WH. The arginine provocative test: an aid in the diagnosis of hyposomatotropism. *J Clin Endocrinol* 1967;**27**:1129–36.

[3] Skare S, Hanssen KF, Kriz V, Torjesen PA. Arginine infusion increases peripheral plasma somatostatin in man. *Clin Endocrinol* 1984;**21**:299–308.

[4] Massara F, Martelli S, Ghigo E, Cammani F, Molinatti GM. Arginine induced hypophosphatemia and hyperkalemia in man. *Diabete Metab* 1979;**5**:297–300.

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ok reviews

ur Atlas of Paediatric Facial Diagno-
By Trevor P Mann. Pp 195: £70.00
back. Clinical Press, 1989. ISBN
5457-001-3.

s is an atlas with details and photo-
hs of 97 different conditions covering
spectrum of childhood disease past and
ent. It is the essence of one man's
erience and sweet it is too. How much
e exciting it proves to be than many of
syndromal texts that now clutter our
ves, many of which we buy because
add a few more conditions, data, or
rences. One does not usually browse
r such books but here is an exception:
one you will buy to read and admire,
inisce with, and above all teach from.
he author splits the book into two
ions, the first to cover neonatal topics
the second those that make their
k later on. In the first part 27 condi-
s are divided under the subheadings of
, hypothermic states, infections,
ellaneous disorders, central nervous
em diseases, and teratological syn-
ne. Part II lists 70 conditions under the
eadings of chromosomal abnormality
dromes, connective tissues diseases,
ocrine system diseases, inborn errors of
bolism, 'extinct' disorders, facial
morphic syndromes, growth distur-
ces, infections, miscellaneous dis-
ers, muscle diseases, nervous system
ases, and pigmentary disturbances. The
for each condition is in turn briefly
orical and then descriptive. The salient
ts that lead to diagnosis are stressed
spiced with references to the indivi-
ls portrayed. For some of the more
mon conditions there are relevant but
t tables that include lists of causes,
ical features, investigative signs, pro-
sive changes, and so on. Three or four
fully chosen references complete the
.

here are 315 photographs, mostly in colour, to illustrate the text. These are of uniformly excellent quality and have been carefully chosen to show, often in one glance, the salient and distinctive features of the condition being described. Sometimes several pictures of the same face in repose, laughter, or tears are used to heighten the appearance and signs while sequential reproductions reflect the changes that take place with growth— or as in the child with systemic sclerosis— recovery.

Unfortunately a reviewer can rarely expect to find his ideal and perfect book and so it is in this case. This one represents after all part of one paediatrician's experience and I suspect only a morsel of that, with each fragment chosen for the quality of the photographs and some particular interest to the author. It should not come as a surprise that in such an atlas some territories are less well charted than others and that occasional important place names have been left out. Sadly it could not be comprehensive.

Who then will want to buy this expensive but beautiful book. The answer is simple— it is every paediatrician, regardless of age, who can afford it. Those that can't should make doubly sure that their unit has one and that is readily available to teachers, juniors, nurses, and students alike to learn from and enjoy.

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Clinical Pediatric Neurology. By G Fenichel. Pp 401: price not stated, hardback. W B Saunders, 1988. ISBN 0-7216-1896-0.

Dr Fenichel has divided this book into 18 presenting complaints which provide the chapter headings. Monoplegia, disorders of ocular motility, and psychomotor retardation and regression are typical examples. Each chapter has between 40 and 120 references selected for ease of access with reviews preferred to original reports. The text is followed by an excellent index and the whole adds up to 400 pages bursting with useful specific clinical information.

With a single author the book has a pleasing consistency of style—which is spare and didactic, particularly on management issues. Sometimes brief discussions with references will allow the reader a chance to form his own opinion from the literature. The approach to diagnosis and treatment is recognisably transatlantic and many British readers will find statements with which they disagree. However, I found both this different view point and the structuring of the subject by symptoms stimulating.

The book refers to many obscure entities but 'infantile bilateral striatal necrosis', 'Machado-Joseph disease', and 'pontobulbar palsy with deafness' seem more digestible when arranged by a prominent presenting symptom than when ranged, as in some texts, like dusty curiosities in an anatomy museum bearing no relationship to their neighbours. This apparent orderliness of this book is partly an illusion as many of these disorders could equally logically have been discussed in other chapters in the same book. Nevertheless, one is left with an impression of a good deal of accurate information and personal experience presented in a readable and clinically relevant fashion.

I think that both general paediatricians and paediatric neurologists will find this book a useful supplement to a disease based account of paediatric neurology: its stengths tend to lie at the points where other texts are weakest.

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Archives of Disease in Childhood, 1989, **64,** 1646

Neonatology—then and now *(CHM Walker)*

Deafness in children of very low birth weight

ALISON D McDONALD

Paediatric Research Unit, Guy's Hospital Medical School, London (Arch Dis Child 1964;**39:**272–7)

The fact that more preterm than term babies were eventually found to have some degree of deafness was recorded at least 10 years before this paper was published. This work, however, confirms the fact that the deafness was mainly:

> 'Moderate or severe high frequency loss with never more than moderate low frequency loss'.

Discussion about aetiology until the middle 1960s ranged around *excessive* oxygen administration, infection, streptomycin, jaundice, and rubella (the latter two being responsible in those days for less than 1% of deaf children of school age). This study, like most reports of this kind at the time, reported the examination of children when deafness was detected by the health visitor or school medical service, therefore it was difficult to attribute cause if there had been intercurrent illness postnatally. in infancy, or early childhood. McDonald, however, found deafness to be related to gestational age of less than 33 weeks and to cyanotic attacks in the neonatal period. No direct relationship was found to intrapartum asphyxia, jaundice, or streptomycin, though it was thought that the condition necessitating treatment with this drug may have been responsible in a few babies.

The discussion ends:

> 'It is suggested that asphyxia during the neonatal period is responsible for deafness in very immature infants, and that the mechanism is neuronal damage by hypoxia'.

Today. We are still trying to determine the exact time at which cochlear damage is sustained. With the advent of auditory evoked brain stem response techniques it has become possible to detect damage in the early postnatal period and so to determine to some extent the relative importance of antenatal and postnatal factors. One such potentially dangerous exposure after birth is that of incubator noise. Not a great deal of attention has been paid to this though, to my personal surprise, having found some incubators with decibel levels surprisingly close to those considered dangerous in industry, this source of damage has been exonerated. Ototoxic drugs are still with us, though short term exposure and careful dosage should prevent injury from these.

So we are thrown back on intrauterine and immediate postnatal factors of which hypoxia, as suggested 25 years ago, seems the most likely culprit. Early detection is important so that stimulation with hearing aids can be initiated as soon as practicable. As it is unlikely that facilities will permit all at risk babies to have evoked response testing it is hoped that the acoustic response cradle will eventually prove consistently reliable as a screening procedure.[1]

Reference

[1] Bellman S. Hearing screening in infancy. *Arch Dis Child* 1986;**61:**637–8.

Alison McDonald graduated at London University (Royal Free Hospital) in 1952, proceeding to MD, Diplomas in Public Health and Child Health and Fellowship of the Faculty of Community Medicine. She must be rather unique in that she has been on the academic staff of three medical schools in London and one in Montreal. After appointments in London as lecturer and senior lecturer at the Royal Free and Guy's Hospitals respectively, she became, in 1964, Associate Professor then Professor in the Department of Epidemiology and Health at McGill University, Montreal. In 1978 she returned to London as Professor and Head of the Department of Epidemiology, St Mary's Hospital Medical School, only to be lost again to Canada in 1981, this time to become Professor in the School of Occupational Health where she is still in practice.

Dr McDonald has researched and written on many subjects relating to obstetrics and the newborn, particularly with reference to congenital defects and developmental problems. She has conducted studies of the Canadian Health Insurance Programme and is currently engaged in producing a series of papers on the effects of work on pregnancy.

No doubt she was one of quite a number of her generation who could be called 'doctors of two (or more) continents'!

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